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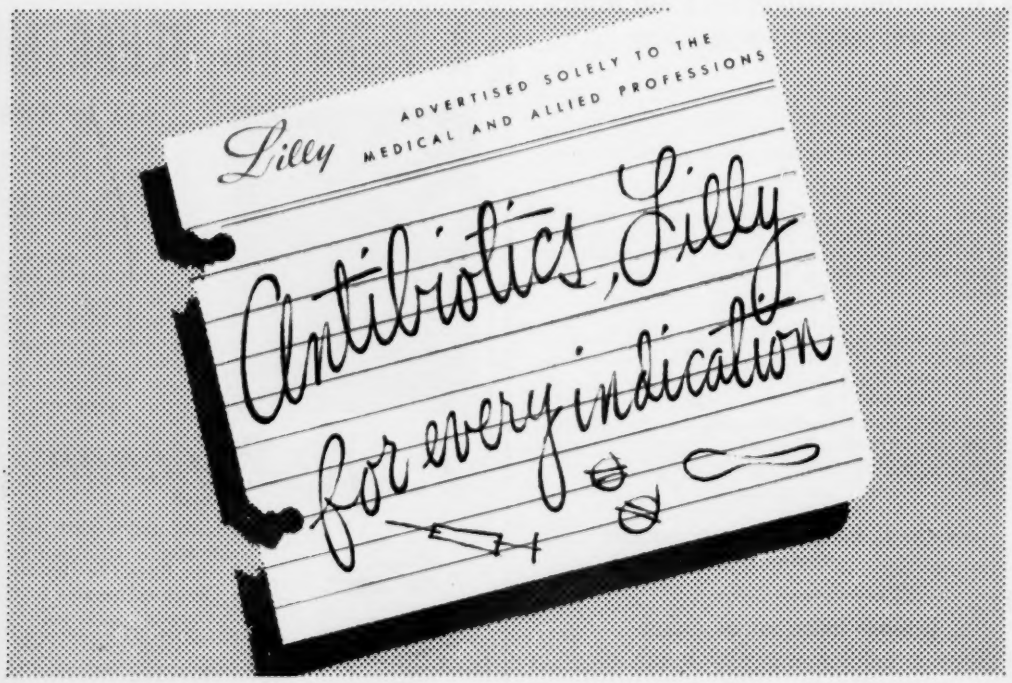

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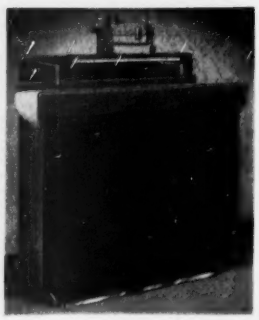

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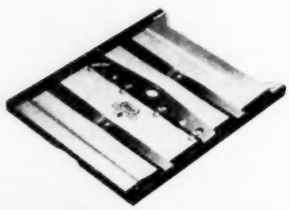

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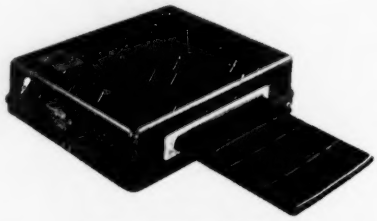

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CLINICAL IMPORTANCE OF EMOTIONAL PROBLEMS IN THE CARE OF PATIENTS WITH BURNS*

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AND BRIGADIER GENERAL RAWLEY E. CHAMBERS, M.C., U. S. A.||

IN a study of victims of the Cocoanut Grove fire, Cobb and Lindemann[1] recorded a high incidence of emotional disturbances soon after burning and concluded that both the psychiatrist and the social worker may play an important role in the care of disaster victims. During the past two and a half years, experience with over 400 burns[2, 3] has shown that serious emotional problems exist in extensively burned patients and that the management of these problems is an integral part of the over-all therapy.

To obtain a better understanding of emotional adjustment in severe burns, 12 patients who had full-thickness burns involving 25 to 45 per cent of the body surface were intensively studied. The average time of complete bed rest in this series was four months.

The purpose of this report is to present the adaptive problems and adaptive mechanisms incident to a severe burn and to show how an understanding of these factors can be readily applied as an integral and essential part of treatment. Detailed psychiatric data on the patients who were studied are the subject of another report.[4]

ADAPTIVE PROBLEMS

When a severely burned patient is admitted to the hospital, he not only is in a state of severe physical pain but also is undergoing serious emotional disturbances. Many of these patients are difficult to manage because of their inability to adjust themselves to their physical status and to their surroundings. Their emotional instability is reflected in their behavior; some are noisy, loud, and demanding, and others are markedly depressed and sullen, and generally refuse to co-operate with the staff. The seriousness of certain adaptive problems varies greatly in different patients.

Primary Problems

The primary adaptive problems are associated with the injury itself. They are: a distinct threat to survival; fear of permanent physical damage and disfigurement; considerable amount of pain and prolonged physical discomfort; frequent general anesthetics and surgical procedures; and a long, tedious convalescence.

Secondary Problems

The primary adaptive problems associated with the injury are complicated by other problems that appear, in varying combinations, in many patients. Prominent examples of these complicating problems are discussed below.

Emotional overtones. At first the emotional overtones associated with the accident may be more distressing to the patient than the actual physical discomfort. This is particularly true when the patient believes that the burn was caused by his own negligence or through the fault of a person he trusted. Patients who have strong feelings of guilt may interpret the injury as punishment. Repetitive anxiety dreams and compulsive rumination about the accident are not uncommonly seen.

Separation from family and friends. Separation from family and friends, which is frequently inevitable in the armed forces, deprives the patient of his main sources of emotional gratification at a time when he needs them most. An overwhelming feeling of loneliness and homesickness often leads to depression and self-pity.

Effect of injury on future plans. The effect of injury on future plans is one of the commonest sources of concern. The patient whose livelihood depends on manual dexterity, for example, is naturally disturbed by burns of the hands. However, the possibility of interference with a non-vocational activity that means a great deal to the patient may be equally disturbing; burns of the

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lower extremities, for example, may be particularly threatening to a young man who has obtained his greatest satisfaction from physical activity.

Feelings of inadequacy. Feelings of inadequacy in comparison with other people may become exaggerated by physical helplessness. Some patients are disturbed by the enforced extreme dependence on others. This occurs chiefly in those who have had serious doubts about their ability to cope with adult responsibility before they were burned. If these doubts have been counteracted by a façade of great independence, the injury necessarily disrupts this previous adaptive mechanism and so leads to tension.

Sexual problems. These are not frequent, but when they occur, they are usually serious. Burns of the genitalia and perineum are not uncommon in the armed forces. Their management generally is relatively simple, but minor burns of the genitalia are more distressing to many patients than serious burns elsewhere. Women are likely to be concerned over their fertility, particularly if the menses are interrupted, as they often are.

Personal rejection. Many patients, particularly women, interpret their injury as a threat to their capacity to be loved by others. These patients are often hypersensitive to the slightest indication of personal rejection and are in constant need of attention.

Hostility. A considerable amount of hostility toward others may be aroused by circumstances connected with the injury or by difficulties in subsequent care. The difficulties of patients who have had serious concern in the past over the handling of hostile feelings may be intensified. This may lead to sullenness, depressive reaction or resentful outbursts.

Adaptive Mechanisms

The many grave psychologic threats of a nearly fatal injury place the patient in danger of being overwhelmed by emotionally painful stimuli. Most patients attempt to avoid these by keeping unpleasant thoughts and feelings out of consciousness (suppression and repression) and by minimizing painful stimuli that do enter consciousness by tight control of all emotions (constriction). The patient's attitude is, in effect, "I will not think about any of these unpleasant things, but, if I cannot avoid them, I will not allow myself to have any feelings about them." A few patients go so far as to avoid any recognition of injury itself (denial). Patients in whom this type of response is very prominent generally have used similar adaptive mechanisms to a lesser extent before injury.

With physical improvement, the need for emergency mechanisms of defense diminishes, and the patient's ability to use more constructive mechanisms of recovery increases. These mechanisms include the patient's co-operative action to help himself; realistic appraisal of his condition; and planning for the future. The fundamental task in emotional rehabilitation is to facilitate these mechanisms in every possible way.

Prevention and Treatment of Emotional Disturbances

Relation with Staff

The patient's confidence in the staff is of the utmost importance. In the early days after injury, many patients are extremely discouraged and see little prospect of recovery except for a primitive, childlike faith in the physician's ability to make them well. This confidence continues to be an indispensable asset in therapy through the difficult months of repeated skin grafts and dressing changes.

When a staff of several physicians is active on the ward, it is essential that one physician assume primary responsibility for all phases of the care of any one patient. Every patient should be able to refer to one of the physicians as "my doctor." This physician should be entrusted with the operations, dressings and blood transfusions, as well as with the management of the emotional disturbances of that patient. A reasonably close, trusting relation with one physician can give the patient a sense of security, even when he is very ill; an indifferent relation with several physicians tends to leave him confused and neglected. A severely burned patient derives little comfort from the realization that the medical staff is highly competent, unless he also has reason to believe that there is a special, personal interest in him.

The common practice of discussing medical problems at the bedside on ward rounds tends to undermine morale. The patient hears fragments of the discussion, including ominous-sounding medical terms, and frequently gets the impression that the doctors are divided, uncertain and not in control of the situation. If the staff is fearful of the outcome of treatment, what hope remains for the helpless patient? These procedures may, at times, have a contagious, harmful effect on the morale and may culminate in a completely disturbed, uncooperative, complaining group of patients.

Relation with Others

In the dismal days after injury, warmth and encouragement of friendly, interpersonal contacts provide the first element of hope. In addition to the medical and nursing staff, attendants, other patients, family and friends can do much to allay fear and to ease tension.

Severely burned patients should be kept on a ward rather than in a private room. When several patients have been involved in the same accident, it is particularly beneficial to group morale to have them on the same ward, or preferably in the same cubicle. Seeing others who have also been badly burned tends to make the patient realize that he

is not in the worst possible condition, that there are others going through the same kind of experience, and that his injuries can be successfully treated.

Visual evidence of the likelihood of uneventful recovery is particularly encouraging in the early phase of hospitalization. On a large burn service, there are always patients in all stages of treatment. Contact with patients who have been burned similarly and who have largely recovered is one of the most important sources of encouragement. Many patients are reassured by seeing photographs that show other severely burned patients at the time of injury and after recovery. This impressive evidence of the probability of ultimate recovery is often more effective than verbal reassurance but cannot take its place: the patient must be told repeatedly that he too will recover. Unfortunately, patients who have recovered from severe burns are often quite reluctant to help those who are acutely ill, for they strive to forget the physical and emotional suffering of their illness, and contact with others who are suffering reminds them, all too vividly, of their own painful experiences. However, even these patients are helpful in that their mere presence on the ward is reassuring to those who are only beginning to recover.

Friendly relations with members of the staff, visitors, other patients and ancillary personnel, including social workers and Red Cross staff, should be encouraged throughout hospitalization. Isolation should be avoided as much as possible.

Early in the course of treatment, reading, motion pictures and other diversional measures are also helpful, especially when the patient is in an emotional state in which he cannot think very much about himself without becoming disturbed. The best way to help the patient is to keep his mind occupied with subjects that do not upset him emotionally. His ability to appraise his situation realistically gradually increases.

Patient's Questions

During the first two weeks, the patient is usually too frightened and bewildered to ask any questions. However, after the acute effects of the injury have diminished, he begins to make inquiries, and it is at this time that an explanation of what can be expected in the ensuing months is most helpful. The physician should be as encouraging as is consistent with honesty. He should never suggest to the depressed patient that, after all, he is lucky to be alive. Although this may be true, it is likely to stimulate resentment in the patient, who usually does not feel lucky but, on the contrary, considers himself a most unfortunate victim of disaster. Most patients have a fear of the consequences of their injury and hesitate to ask questions. Anxiety can frequently be avoided if questions are anticipated by the physician. Patients are usually most anxious to know about the expected length of hospitalization and the effects of the injury on their appearance and function. The possibility of permanent physical disfigurement may be particularly distressing to women.

In general, it is impossible to give answers with any high degree of certainty. It should be explained that any statement of what to expect is merely a rough estimate based on experience. Prevarication or evading of the issue is ill advised, since the patient eventually learns the truth and his confidence in the physician is then undermined. The encouraging aspects of the expected result should be emphasized. For instance, even deep facial burns rarely cause permanent damage to eyesight. Edema of the lids rapidly closes the eyes, and patients who have facial burns are frequently terrified by the idea of the possible loss of vision. Emphatic reassurance on this point, which can usually be given truthfully, is very helpful. However, it is not sufficient to give explanations once or twice, for the patients are often afraid to believe encouraging explanations and, like frightened children, must be reassured again and again. Simplicity, repetition and an attitude of genuine interest in the patient are the essential elements of good explanation; vagueness leads to doubts and fears.

Pain

The treatment of a severe burn entails some pain and frequent minor physical discomfort over a long period. However, physical pain is considerably less severe than is generally supposed; on the other hand, emotionally induced pain is a much more serious problem than is generally recognized.[5] Patients frequently do not distinguish between physical pain and emotional tension and report all discomfort, regardless of origin, as pain. It is of great importance to realize that the patient needs not only relief of pain but relief of fear as well.

If, as frequently happens, all the patient's complaints are treated with narcotics, he may rapidly become addicted, at least emotionally. There is no better way of making a patient completely unmanageable than by giving him frequent injections for emotionally induced pain. In patients whose emotional needs are neglected, regressive behavior sometimes occurs, with prominent manifestations of crying, moaning, complaining and demanding. The patient's behavior resembles that of an extremely frightened child. Prolonged regression in predisposed persons may lead to chronic invalidism. All this, however, can be prevented.

Ordinarily, the prevention of persistent emotional disturbances is not difficult if sufficient interest is present, but it does require that the physician spend a considerable amount of time with the patient and be attentive to emotional factors throughout hospitalization. An effort should be made to discuss the patient's problems in a friendly, noncritical way, with a view toward understanding some of the emo-

tional sources of his concerns and complaints. This need not involve any extensive exploration of the patient's personality, but it does require thoughtful consideration of his actual situation and his personal reaction to it. It is particularly important to have a detailed interview whenever he shows signs of emotional disturbance. During the interview it is often helpful for the physician to sit at the bedside rather than to stand by the bed, even if time is short.[6] This tends to convey the comforting impression that the physician is giving his undivided attention to the patient's problems.

Pain that requires analgesic drugs is a prominent feature only after grafting procedures or extensive dressing changes. The patient soon learns which procedures are painful and which are not, and he can be taught to request analgesia only for physical pain. When the patient is disturbed emotionally, a short-acting, injectable barbiturate, such as sodium pentobarbital, is frequently useful as an adjuvant to psychotherapy.

Facilitating Recovery Mechanisms

A large part of what has already been mentioned bears on the therapeutic value of encouraging adaptive mechanisms. The patient's capacity for co-operative action to help himself, though quite limited at first, increases progressively. Since the maintenance of nutrition is a crucial part of burn therapy, it should be suggested that eating the prescribed and supplemental foods is one way in which the patient can materially aid his recovery. Another example of the opportunity for direct action is found in the patient whose hand burns have healed but who still has large open wounds elsewhere. By concentrating his efforts on active motion of the hands, he can do much to promote more rapid and complete return of function. Except in rare cases, bullying of the patient into co-operation by threatening him with the dire consequences that failure to co-operate might entail should not be attempted. It is best to emphasize the positive aspects as much as possible.

The patient should be assisted in a realistic appraisal of his condition. In this evaluation, he should not exaggerate his disability and so withdraw from his ordinary activities and relations, nor should he refuse to accept reasonable limitations made necessary by residual effects of his injury. When an accurate and hopeful appraisal is reached, he can begin to plan for his future life. He should be encouraged in this and helped as needed to carry out his plans. Matters of insurance, family arrangements and future employment must be considered. Medical social service can often be of assistance in this connection, as well as in many of the other problems of rehabilitation.

In every feasible way, the patient should be helped to understand that he will again be an active, constructive member of society and not an invalid, even though his way of life may be somewhat changed.

Discussion

Intensive investigations of many aspects of burns during the past decade have produced great improvement in therapy. Psychosomatic aspects of burns, however, have been given surprisingly little attention, although this approach to disease has been applied extensively in other conditions. Clinical experience has demonstrated that emotional factors have considerable influence on the patient's rate of recovery. Of course, the patient whose progress is satisfactory has less reason to be discouraged than the patient whose progress is slow. In some patients, however, improved morale appears to precede physical progress.

Although psychiatric consultation is necessary and helpful in cases of persistent or serious emotional disturbance, the observations of this study indicate that the emotional factors in patients with burns can be competently managed as a part of comprehensive clinical treatment by the nonpsychiatric physician. The physician in charge of the patient's care is in a key position; his action are so important that he can exert a profound effect on the patient's mental state. In recent months, scrupulous attention to emotional welfare has yielded encouraging results in terms of more rapid recovery and restoration of function. The axiom that the welfare of the patient with burns is directly related to the amount of care that he is given also applies to psychologic adjustment.

Although burns are an unusually severe form of injury, many of the observations of this study are probably applicable to other forms of severe injury, particularly when an overwhelming injury is complicated by prolonged convalescence and the possibility of permanent disability.

Summary

Experience in the care of more than 400 patients with burns has shown the importance of emotional problems in clinical management.

Detailed psychiatric studies on 12 patients who had full-thickness burns involving 25 to 45 per cent of the body surface emphasized the fact that the primary adaptive problems were threat to survival, fear of disfigurement, prolonged physical discomfort, frequent surgical procedures and long convalescence.

Initially, adaptive mechanisms used by patients were suppression and repression, constriction and denial. During the period of recovery, the constructive mechanisms of co-operative action, realistic appraisal and planning for the future were common.

Contact with patients who had been burned similarly and had largely recovered proved an important source of encouragement. Reassurance

was gained from photographs of similarly burned patients before and after recovery.

Physical pain appeared to be considerably less severe than is generally supposed, and, contrariwise, emotionally induced pain and anxiety were prominent features.

It is important to assist the patient's recovery mechanisms in every possible way. The patient must be helped to understand that he will again be an active and constructive member of society.

Recovery and restoration of function of severely burned patients are favorably influenced by careful attention to the prevention and treatment of emotional problems.

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PARAMYLOIDOSIS WITH DIABETES MELLITUS AND GASTROINTESTINAL HEMORRHAGE

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PHILADELPHIA

PARAMYLOIDOSIS (or primary amyloidosis)[1] is a rare condition, only about 70 cases having been reported in the literature. Paramyloid deposition is widespread in the body, and as a result its clinical manifestations are protean. The case reported below is interesting in that it further illustrates this point, and presents prominent involvement of the gastrointestinal tract and pancreas, with resulting gastrointestinal bleeding and diabetes mellitus.

A review of the literature on amyloidosis and paramyloidosis discloses that classification of the several types is unsettled. Indeed, there is evidence that there may be only a minor, though fundamental, difference between these two conditions.[2] It is not our purpose to discuss these points or to review the details of the subject, for there are excellent review articles that cover the disease, its pathogenesis, classification and varying clinical picture in detail.[2-6] It may be said, however, that the criteria for differentiating the types are those of distribution and staining characteristics of the amyloid substance, and the presence, absence or type of underlying process — that is, the pathogenesis.

In general, paramyloidosis (or primary amyloidosis) is the type in which amyloid is mainly present in the mesenchymal tissues, the amyloid stains atypically with at least some of the usual amyloid stains, and the pre-existing pathologic process is obscure. The following case showed amyloid of this type.

Case Report

A 57-year-old Negro warehouse laborer was first admitted to the Metabolic Ward of the Philadelphia General Hospital on April 4, 1951, because of massive hematemesis. He was known to have had diabetes for 3 years and required about 50 units of insulin daily.

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The past history was significant in that he had been operated on in 1931, apparently because of a peptic ulcer. The nature of the procedure was not known. In the past he had used alcohol excessively, but denied any ingestion of alcohol since the onset of his diabetes. He had never been known to have tuberculosis. There had been weight loss from 190 to 141 pounds during the 10-year period preceding the present admission. Otherwise, the past history was not remarkable.

The patient had been asymptomatic until 1950, when he was admitted to another hospital, where the diagnosis of a peptic ulcer had been made by x-ray studies, and he had been treated accordingly, with a good symptomatic response.

For 2 weeks before the episode of hematemesis, he had been having steady epigastric pain, which was worse 15 minutes after meals and was associated with nausea, fullness and flatulence. The pain was relieved only for a few minutes by milk. In addition, on admission there were symptoms of anemia — dizziness, palpitations, weakness and dyspnea on exertion.

Physical examination revealed a light-complexioned Negro, 6 feet tall, showing moderate wasting and pallor but in no acute distress. There was no sweating. There were small skin nodules (of 2 or 3 months' duration) over the forehead and back. The right pupil was dilated, fixed and larger than the left, which reacted consensually to light. (These pupillary abnormalities were never explained by ophthalmologic or neurologic consultants.) The fundi were normal. The heart was not enlarged, showing a normal sinus rhythm and no murmurs. The chest was clear. There was a scar on the upper abdomen. The liver was enlarged, extending from the 5th rib to 4 fingerbreadths below the right costal margin in the midclavicular line. The edge was smooth, hard and sharp and was nontender. The spleen was not palpable. There was no ascites, no edema and no palmar erythema. There were no cutaneous angiomas. Rectal examination was negative, as was a later proctosigmoidoscopy. Otherwise the physical examination was not remarkable.

The temperature was 99.6°F., the pulse 104, and the respirations 24. The blood pressure was 90/66 (later rising to 110/90).

The blood sugar was 252 mg. per 100 cc. on admission, gradually falling to less than 190 mg. per 100 cc. during the day. The carbon dioxide combining power was 51 vol. per cent, and the blood urea nitrogen 51 mg., and the hemoglobin 7.0 gm. per 100 cc. Serologic tests for syphilis were negative. The results of liver-function studies are shown in Table 1. Spinal-fluid examination was negative except for a protein of 170 mg. Alkaline phosphatase was 0.65 units and inorganic phosphate 3.97 mg. per 100 cc. The hemoglobin rose to 12.5 gm. per 100 cc. after treatment. Urinalysis showed a specific gravity of 1.022, a negative to + test for albumin, and occasional white cells and, on one occasion only, innumerable red cells in the sediment. No casts were noted. The 24-hour urinary sugar was 4.7 gm. per 100 cc.

After admission the patient received whole-blood transfusions, ferrous sulfate and a rigid ulcer regimen. There was

no further bleeding, and the diet was gradually liberalized (90 gm. of protein, 110 gm. of fat and 240 gm. of carbohydrate). The diabetes was brought under control with some difficulty, finally being fairly well regulated with 20 units of protamine zinc insulin and 20 units of regular insulin (separately) in the morning.

On April 30 a biopsy of a skin nodule on the trunk was reported as demonstrating fibrosis. A subsequent examination of the section revealed amyloid in the dermis. On May 8 a liver biopsy (aspiration) showed all sinuses of the liver to be lined with a thick layer of material containing fat and similar in appearance to amyloid. This material stained blue with trichrome and with the mucopolysaccharide stain of poorly regulated diabetes, with polydypsia and polyuria. Examination showed no essential change from the previous admission. The liver was still enlarged, the spleen not palpable, and there was no edema or ascites. The diabetes was again brought under control, at first with some difficulty. Later insulin requirements dropped from about 40 to about 20 units a day. The patient's weight continued to decrease, reaching a low of 129 pounds. He was given the same treatment as noted above, in addition to choline, 1 gm. three times a day. He ate very poorly.

The blood sugar was 552 mg. per 100 cc., and carbon dioxide combining power 36 vol. per cent. Subsequently, the blood sugar level fluctuated widely, with gradually diminishing

TABLE 1. *Results of Liver-Function Tests.*

DATE	TOTAL PROTEIN	ALBUMIN-GLOBULIN RATIO	CEPHALIN FLOCCULATION	THYMOL FLOCCULATION	THYMOL TURBIDITY	BROMSULFALEIN RETENTION	SERUM BILIRUBIN	PROTHROMBIN
1951	*gm./100 cc.*					%	*mg./100 cc.*	%
April 5	6.0		0	0	0	5	0.69	100
	6.5	5.2/1.3						
April 10	7.2	5.4/1.8	++	0	0	5	0.35	100
May 2								98
October 16			0	0	0	7	0.20	
October 26	7.7	5.3/2.4						
November 2	7.0							
November 21						21		
November 27	7.3	3.7/3.6					0.63	

Ritter and Olsen. The liver cells contained fat, pigment and a small amount of glycogen. No iron, bile pigment or cirrhosis was present.

An electrocardiogram showed a normal sinus rhythm, low voltage in the indirect leads and terminal T-wave inversion in Leads V_3, V_4 and V_5. An orthodiagram demonstrated the transverse diameter of the chest to be 29.8 cm. and that of the heart as 14.0 cm.

X-ray examination of the upper gastrointestinal tract on April 11 revealed no abnormalities. Another study showed a deformity at the apex of the duodenal cap, and, though no ulcer niche was found, it was concluded that there was a duodenal ulcer. A barium-enema examination was negative. A roentgenogram of the chest disclosed small, irregular areas of calcification in the right second anterior interspace and at the level of the fourth rib in the anterior axillary line, but was otherwise normal, as was an intravenous pyelogram. Calcifications were demonstrated in the pancreas. There were hypertrophic changes in the spine.

The patient was discharged on May 25, 1951, much improved, on a liberal ulcer and diabetic regimen. He had been afebrile throughout the hospital course.

After discharge the patient returned to work for about 2 weeks. Then he began to notice weakness, fatigability and shortness of breath on exertion. He had to stop working, but did not return to the clinic for another 2 months. The diabetes had been poorly controlled. Examination then revealed marked pallor, epigastric tenderness and a blood pressure of 100/80, but no other changes from those noted above. Therapy consisted of a diabetic ulcer diet, parenteral administration of crude liver extract (twice weekly), ferrous sulfate, tincture of belladonna, supplementary vitamins and aluminum hydroxide gel—essentially the regimen used in the hospital. The patient continued to lose weight, complained of anorexia, weakness and extreme fatigability, and was obviously losing ground.

Laboratory studies showed the hemoglobin to have dropped from 11.4 to 7.9 gm. per 100 cc., with normocytic red cells. Urinalysis demonstrated a specific gravity of 1.022 and a + test for albumin, with 1 or 2 white cells and 0 to 2 casts (granular). The results of liver-function studies are presented in Table 1. A gastrointestinal series revealed esophageal varices, no ulcer and a duodenal diverticulum. One stool examination (Hematest) was negative for occult blood. An electrocardiogram disclosed changes similar to those noted previously, but improvement in the T waves.

Because of the evident deterioration, the patient was again admitted to the hospital on November 2. He complained mainly of profound weakness, but also of nausea, severe anorexia and dyspnea on exertion. There were symptoms of insulin requirements. The blood urea nitrogen was 37 mg. per 100 cc. on admission, and a later determination was 24 mg. per 100 cc. A bone-marrow aspiration on November 27 showed slight lymphocytosis, slight plasmacytosis, and slight erythroid hypoplasia. Another roentgenogram of the chest disclosed no change. An electrocardiogram was reported as normal, and the orthodiagram was considered to indicate no cardiac enlargement. Another barium-enema examination was negative. A gastrointestinal series demonstrated 40 per cent gastric retention at the end of 2 hours, with pancreatic calcification but no evidence of a duodenal ulcer or of esophageal varices. An esophagoscopic examination was negative.

Bleeding and clotting times were normal. The cholesterol was 240 mg. per 100 cc., with 66 per cent esters. Stool examination was negative on one occasion for occult blood. The hemoglobin fluctuated around 10 gm. per 100 cc. A 24-hour urinary sugar was 1.4 gm. Urinalysis revealed a specific gravity of 1.029 and a trace of albumin, with a few red and white cells in the sediment.

On December 6 biopsy of a left axillary lymph node showed marked hyperplasia of all structures of the node, with no evidence of amyloidosis in the node itself. The perinodal fat, however, contained deposits of a pink-staining material resembling amyloid. During the night a considerable hemorrhage occurred from the operative site. On the following morning, during a gastric analysis, about 50 cc. of blood was aspirated. The tube was removed, and the test discontinued. On the next night hematemesis occurred, the patient went into shock, and blood transfusions were needed to stabilize the situation. At that time determinations of the bleeding and clotting times, capillary fragility tests and a platelet count were within normal limits. Vitamin K was administered parenterally in massive doses, though the prothrombin-time determinations had been normal and were not repeated. On the following day, because of continued bleeding, an exploratory laparotomy was performed. The stomach was opened, and bleeding was found from an area of erosion high in the stomach, as well as from esophageal varices. No type of resection was possible because of the patient's critical condition and the technical difficulty presented by the enlarged, hard liver. Biopsy of the liver and gingiva was performed.

The liver cords were greatly atrophic owing to the deposition between them of an amyloid-like but methyl-violet-negative material. A gingiva biopsy was normal except for the deposition of an amyloid-like, methyl-violet-negative material in the walls of the arterioles. Postoperatively the patient continued to bleed, and in spite of intensive supportive measures died in shock.

At autopsy, aside from a recent surgical incision in the abdomen and palpable supraclavicular and axillary lymphadenopathy, no external abnormalities were noted. The visceral pleura of both lungs was speckled with translucent, pink, hard plaque-like lesions 1 to 3 mm. in diameter. There were scattered acute and subacute adhesions of the abdominal organs and mesentery. A small amount of free blood was found between the layers of the small-bowel mesentery; 100 cc. of free blood was in the abdomen. There was a subserosal hemorrhage in the jejunum, with deep-purple staining of the stomach, duodenum and transverse colon.

The heart weighed 310 gm. The right atrium presented numerous hard, pink, subepicardial plaque-like lesions from 1 to 3 mm. in diameter, similar to those on the visceral pleura. The other chambers of the heart were free of these lesions.

The spleen weighed 330 gm. and measured 10 by 7 by 5 cm. Its consistence was firm and rubbery, and it was resistant to section, which revealed hard, slimy surfaces. On microscopical study both the splenic cords of the red pulp and malpighian bodies contained large amounts of paramyloid. The splenic cords were greatly thickened by the opaque infiltration but retained the structural pattern of the red pulp. The malpighian bodies were diffusely infiltrated, and many were completely replaced by the large amorphous masses.

The hilar and abdominal lymph nodes were white and hard in consistence, but only a few were greater than normal in size.

On microscopical examination some nodes showed a moderate degree of fibrosis only. The hilar nodes revealed thick-

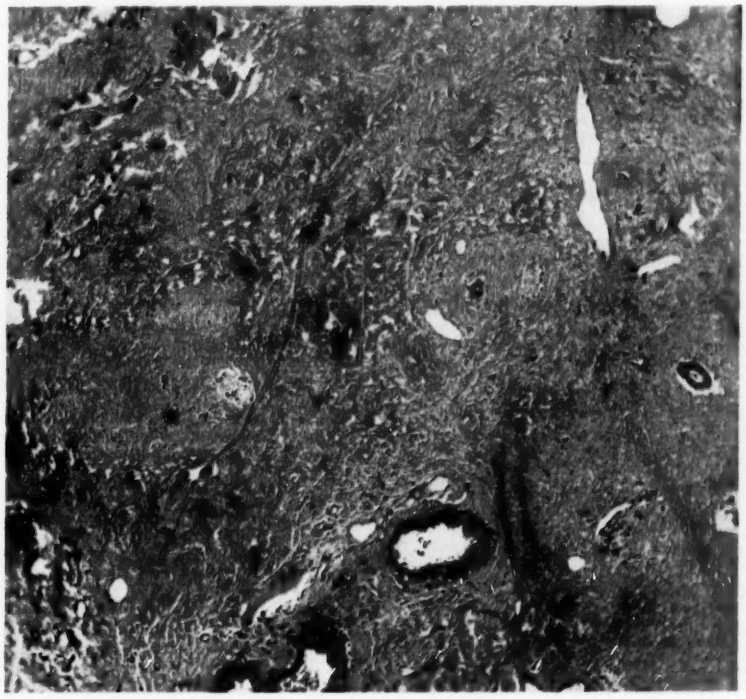

FIGURE 1. *Photomicrograph of Pancreas, Showing Extensive Amyloidosis (X100). Note the few remaining ducts, with obliteration of the acinar tissue.*

The valves, myocardium and coronary arteries appeared normal. Microscopical examination disclosed small, patchy deposits of paramyloid in the ventricle surrounding muscle fibers, in some areas infiltrating and completely replacing muscle groups and in others involving only the walls of the small blood vessels. The atrial muscle showed involvement similar to that of the ventricle, with areas of almost complete replacement of muscle fibers by large, opaque, pink, refractile masses. In addition to these changes there were nodular subepicardial masses of paramyloid previously identified grossly. In other areas the epicardial fat was also replaced by amorphous, pink masses.

The right lung weighed 570, and the left 400 gm. Both were severely congested, especially at their bases, and on section revealed innumerable hard, pink, plaque-like lesions, 1 to 3 mm. in diameter. On microscopical examination small amounts of paramyloid were found in the walls of the pulmonary vessels and in scattered alveolar septums, but the major deposition consisted of large, amorphous, pink masses completely replacing the normal alveolar architecture.

ening of the medullary cords, which were diffusely opaque, pink and devoid of cells. In other areas large nodular deposits replaced the normal structural pattern.

The liver weighed 2900 gm. Grossly it was orange tan and hard in consistence, with a finely granular surface. It was rubbery and resistant to section, with an indistinguishable parenchymal pattern. Microscopical examination of the liver revealed a diffuse infiltration of paramyloid along the walls of the sinusoids, with compression and atrophy of liver cells in focal areas. The degree of involvement was severe, with the staining characteristics described above.

The gall bladder was normal in size, with a dark-orange mucosal surface. This surface was almost completely covered by numerous, irregular, firm but ragged mucosal projections, varying from 4 to 7 mm. in diameter. These projections were also over the mucosal surface of the proximal cystic duct. On microscopical study the paramyloid was deposited in small amorphous masses in the lamina propria mucosae, and in large patchy infiltrating and polypoid masses extending through and replacing the entire wall.

The pancreas was normal in size but was extremely hard in consistence, with grossly calcified areas. On microscopical examination the paramyloid formed large diffuse and nodular amorphous deposits, replacing practically all the acinar and island tissue (Fig. 1). There were areas of calcification. The parenchymal pattern was completely destroyed.

The esophagus presented a few prominent varices at the lower end. The stomach contained a massive amount of dark-red and black blood, and there were numerous subacute gastric ulcerations 3 mm. to 1.5 cm. in diameter along the greater curvature and posterior wall of the fundus and body of the stomach. A gastrojejunostomy site (apparently from the operation performed in 1931) appeared normal. The 8-cm. surgical incision on the anterior antral wall was intact, with hemorrhage between the layers at this site. An old, healed duodenal ulcer was present in the first portion of the duodenum. Microscopical sections of the duodenum revealed a healed ulcer and superficial mucosal ulcerations, with submucosal hemorrhages.

The stomach showed a diffuse chronic inflammatory infiltrate with mucosal and submucosal ulcerations and severe hemorrhage extending between the layers of the wall. Both stomach and duodenum contained paramyloid deposits in patchy masses in the lamina propria and submucosa, particularly surrounding and replacing many of the Brunner and gastric glands.

The jejunum disclosed only a severe chronic inflammatory infiltration.

The right kidney weighed 250 gm., and the left 200 gm. Both were larger than normal, deep pink and firm to rubbery in consistence, with a hard, flat surface on section. The cortexes were wider than normal, with prominent vascular markings. On microscopical examination the paramyloid was seen as deposits in the walls of the arterioles, which were thickened and opaque, as nodular masses replacing parts of the glomeruli and as small irregular patchy interstitial infiltrations, particularly in the cortex and producing compression of the tubules in areas.

The adrenal glands together weighed 16.5 gm. and were firm in consistence, with indistinguishable corticomedullary layers on section. Microscopical examination showed the cortex to be diffusely infiltrated with paramyloid, with compression and atrophy of the cells. The small vessels in the medulla were also opaquely thickened by amyloid deposits.

Discussion

The case presented above is an example of systemic paramyloidosis involving the usual sites of this disease: the heart, blood vessels, lungs, skeletal muscles and gastrointestinal tract. Prominent involvement of the parenchymatous organs, which is also present, is more common in secondary amyloidosis. That there was massive parenchymatous involvement, mainly of the liver, is somewhat unusual but not unknown in the primary type.[3, 4] In general, the reported cases of massive liver involvement have been unassociated with jaundice, and liver-function studies have indicated little or no impairment of function. In 10 reported cases[3] there was marked hepatic infiltration with normal or only slightly impaired function as tested by the usual methods. A review of the liver-function tests in the case reported above gives evidence of impaired function only late in the course of the disease by the bromsulfalein retention and the serum protein changes. There was no jaundice at any time. Jaundice has been reported,[3] its mechanism being unexplained. Jaundice is even more infrequent in secondary amyloidosis of the liver, and there is a similar lack of impaired function as measured by the standard clinical tests.[3] Amyloid disease of the liver should therefore be considered in the differential diagnosis of hepatomegaly without jaundice and with minimal or absent impairment of hepatic function as measured by the usual clinical tests.

It is interesting that there was almost complete replacement of the pancreas (both island and secretory parenchyma) by the amyloid, with calcification that was identified by roentgenogram. Calcification and ossification have long been known to occur in amyloid.[7] In all likelihood, the diabetes resulted from the replacement of the pancreatic islands by amyloid. There were no clinical symptoms of insufficiency of the external secretions of the pancreas, though they were undoubtedly decreased markedly. No laboratory studies were done in this regard. It is possible that the patient's abdominal pain was related to the chronic pancreatitis.

An extensive survey of the medical literature in English fails to reveal another case of paramyloidosis with severe parenchymatous involvement of the pancreas and diabetes mellitus. Because of the high insulin requirements of this patient, it is possible that factors other than islet-cell deficiency caused the diabetes in this case, however. Usually, only the vessels of the pancreas are involved in paramyloidosis, though parenchymatous involvement has been reported.[8]

Clinically, interest was drawn to the large, hard, sharpedged, nontender liver, which, until shortly before death, showed normal function. However, the chief additional manifestation was gastrointestinal hemorrhage, which resulted in death. The bleeding occurred from points in the gastric mucosa where amyloid was heavily infiltrated with overlying erosions. Such gastrointestinal hemorrhages have frequently been reported in this disease.[9]

Curiously enough, this patient also had esophageal varices, undoubtedly secondary to the extensive amyloidosis of the liver with portal hypertension. Bleeding from the varices was identified at operation.

Because of the difficulty of establishing the diagnosis, even when it is suspected, biopsy must be used to demonstrate amyloid, and liver biopsy may be necessary if more readily accessible tissues are not involved. The liver biopsies in this case demonstrated the atypical amyloid, as did the gingival, lymph node and skin biopsies. It is interesting that the abdominal lymph nodes were more involved than the peripheral nodes. Fat, skeletal muscle and the mucosa of the nose, pharynx, paranasal sinuses and larynx have been used as biopsy sites to estab-

lish the diagnosis. Other more unusual sites have been reported (vagina,[10] tendons,[3] stomach[11] and nerves[12]). In general, one should biopsy any available suspicious lesions.

It has been previously noted that certain electrocardiographic changes occur in amyloid disease of the heart.[3] These consist of low-amplitude, sometimes notched, QRS complexes in the standard leads, with flat or diphasic T waves. The precordial leads show low amplitude of the QRS complexes over the right and left precordium, with flat or inverted T waves over the left precordium. It is recognized that these abnormalities are not specific for amyloid disease, other conditions producing similar changes. In the case presented above, the standard leads showed low amplitude, and the T waves changes over the left precordium, but in the first tracing only. A subsequent tracing demonstrated improvement, and the last was within normal limits. In view of the improvement to normal and the relatively minor involvement of the heart pathologically, the electrocardiographic changes were probably not significant of amyloid disease of the heart in this case.

Renal involvement was not a significant part of the clinical picture, though albuminuria occurred, and there was slight elevation of the blood urea nitrogen.

It is interesting to call attention to the changes in the plasma proteins during the course of the illness. There was a fall in the albumin fraction late in the disease, with a rise in the globulin fraction, and the total protein remained normal. This suggests a late reactivation of the process that results in amyloid deposition.

Summary

Another case of primary amyloidosis is added to those already reported in the literature. This patient clinically showed diabetes mellitus, hepatomegaly and gastrointestinal hemorrhage, the last causing death. The diabetes was probably the result of extensive replacement of the pancreas by amyloid that was calcified. Although the disease was of the primary type, there was extensive parenchymatous involvement of the liver, pancreas, spleen and kidneys.

At a staff meeting of the Long Beach Veterans Administration Hospital held on October 9, 1952, Dr. Gurth Carpenter discussed the "hyperglobulinemic purpuras," a classification that might well include the purpuric, manifestations and bleeding of primary amyloidosis, in which there is often an elevated globulin fraction. Although Dr. Carpenter, who has extensively studied purpuras of this type, was not aware of any relation to these purpuras, the possibility of such an explanation for the bleeding tendency in amyloid disease remains. Perhaps future investigations will conclusively settle this point.

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PULMONARY EDEMA IN ACUTE OPIUM INTOXICATION*

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BOSTON

ACUTE opium intoxication is not commonly seen in American medical practice. However, two phenomena may well portend an increased incidence in the near future. Throughout the United States evidence of widespread drug addiction appears almost daily. The problem of drug addiction has also become most important to American troops stationed in certain overseas areas.[1] The exposure of the uninitiate to opium derivatives leads to accidental and intentional overdosage. The purpose of this report is to stress the occurrence

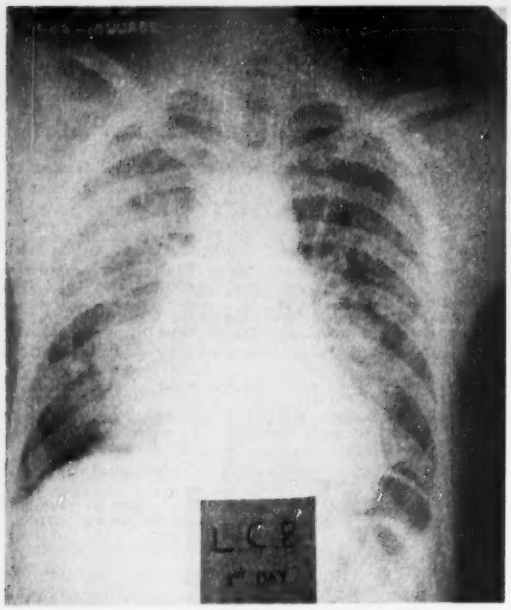

FIGURE 1. *Roentgenogram of the Chest on the First Hospital Day, Showing Diffuse Hazy Patches of Increased Density Extending from the Hili and Obscuring Both Lung Fields, Most Noticeably on the Right.*

Note the marked prominence of both hili and the relative sparing of extreme portions of the apexes and bases.

of pulmonary edema in acute opium intoxication, and its pathogenesis, diagnosis and treatment. An illustrative case report is presented.

CASE REPORT

A 21-year-old soldier was admitted to a station hospital on August 25, 1951, at 3:30 a.m. He had been found unconscious in an alley with a hypodermic syringe and needle nearby.

Physical examination revealed a well developed and well nourished man who was comatose and deeply cyanotic, with respirations of 1 a minute. Fresh needle-puncture wounds were present in both antecubital fossae. There was no evidence of trauma. The pupils were markedly constricted and did not react to light. The neck was supple. There was no cervical-vein distention. The lungs were clear

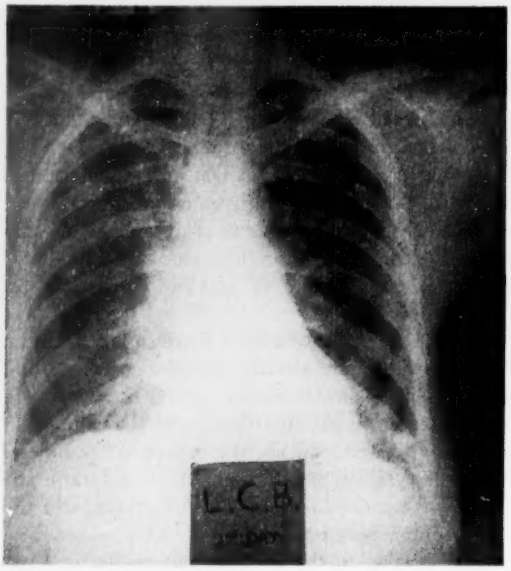

FIGURE 2. *Roentgenogram on the Second Hospital Day. There is marked clearing of the lungs, but patches of increased density persist, most noticeably on the right. There is moderate prominence of the hili, especially the right hilus.*

to auscultation. The heart was normal in size, with sounds of good quality, regular rhythm and a rate of 80. The blood pressure was 116/58.

Treatment was initiated with oxygen by Boothby mask, artificial respiration, caffeine and atropine. The patient's color rapidly began to improve, and after ½ hour spontaneous breathing began at a rate of 6 respirations a minute. A few minutes later mild clonic convulsions occurred. During the next 6 hours he gradually became more responsive but was still stuporous. The respiratory rate rose to 16 a minute. The nail beds were still slightly cyanotic. He began to cough up small amounts of thick, rust-colored sputum. Later in the day, scattered rales were noted in the lungs for the first time. A roentgenogram of the chest (Fig. 1) showed diffuse hazy patches of increased density extending outward from the hili, obscuring both lung fields but most noticeably on the right, with relative sparing of extreme portions of the apexes and bases. There was marked prominence of both hili. Nasal instillation of oxygen, intravenous injection of fluids and prophylactic chemotherapy were continued.

By the 2d hospital day the patient was alert, afebrile and asymptomatic, with no cyanosis, and required no further oxygen therapy. A roentgenogram of the chest (Fig. 2) revealed marked clearing, but patches of increased density persisted, especially on the right. The remaining hospital stay was uneventful. On the 4th hospital day there was

*A preliminary report of this paper was presented on April 18, 1952, at the Far East Command Medical Conference in Kyoto, Japan.

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further clearing of the lung fields, but small patchy areas of density remained. There was mild prominence of the right hilus (Fig. 3). By the 8th hospital day the chest appeared normal (Fig. 4).

Discussion

Acute opium intoxication is seen in both the addict and the nonaddict.[2] The diagnosis should be suggested by the classic triad of coma, greatly depressed respirations and pin-point pupils. An appropriate history, the presence of needle-puncture wounds and the finding of opium derivatives in urine or gastric contents are confirmatory. The case presented above was one of a number encountered in an Army hospital in Japan in which pulmonary edema was part of the clinical picture of acute opium intoxication. Unless pulmonary edema is expected or is detected on routine x-ray study of the chest, its presence may not be appreciated. The pulmonary edema is unlike that associated with cardiovascular disease; rales and other direct signs, except cyanosis, are rare. The edema is evidently chiefly interstitial, with no marked alveolar component, except as noted below. The orthopnea and dyspnea that characterize the pulmonary edema in acute failure of the left ventricle are not present. In none of the cases has pressure in the pulmonary circulation sufficiently increased to cause failure of the right ventricle or to produce signs, such as cervical-vein distention, indicating imminent failure.

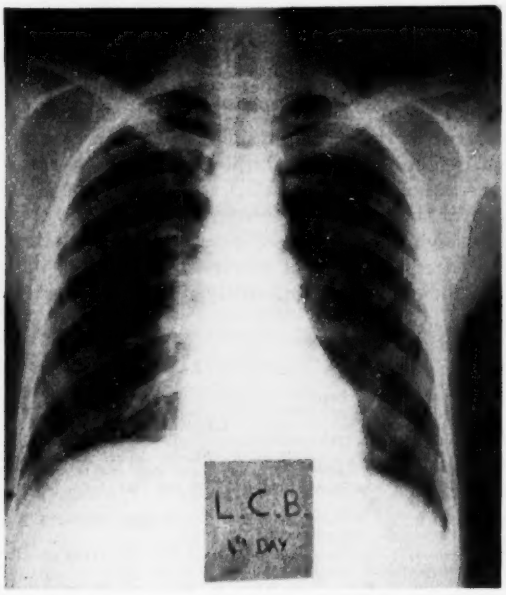

Figure 3. *X-ray Appearance of the Chest on the Fourth Hospital Day.*
Further clearing of the lung fields is seen. Small patchy areas of density remain. There is mild prominence of the right hilus.

The mechanisms of pulmonary edema in acute opium intoxication are not clear. The cases observed represent intoxication by a single intravenous injection of almost pure heroin. Heroin is four or more times as depressant to the respiration as morphine. The marked depression of the respiratory center and the possibility of direct pulmonary irritation after intravenous administration are of possible etiologic significance in the production of pulmonary edema. The clinical picture of acute opium intoxication is similar with the different opium derivatives; pulmonary edema also occurs in poisoning by the oral route.[2-4] It is interesting that morphine is helpful in the treatment of pulmonary edema associated with failure of the left ventricle, but it can also produce pulmonary edema.

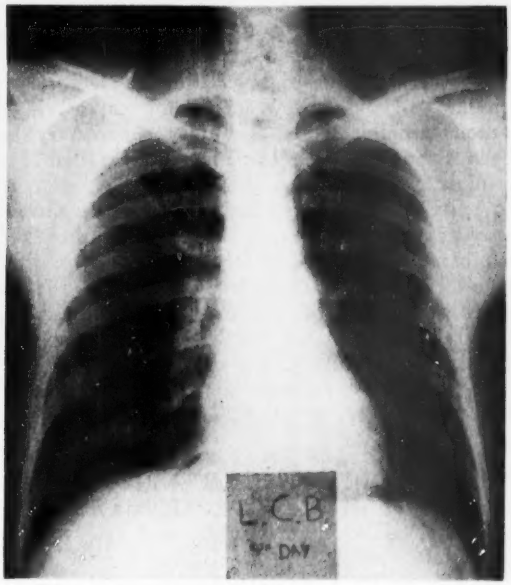

Figure 4. *Roentgenogram of the Chest on the Eighth Hospital Day.*
The chest now appears normal.

The importance of the pulmonary edema of acute opium intoxication is indicated by the response to therapy. On occasion when the respirations have increased toward normal and the patient has become responsive, discontinuance of intensive oxygen therapy results in almost immediate loss of consciousness. There is no longer enough oxygen tension to overcome the barrier interposed by the pulmonary edema. The pulmonary edema causes marked impairment of respiratory function, accentuating and perpetuating the primary depression of the respiratory center. The net effect of this vicious circle is a profound anoxic anoxemia, which

is the direct cause of death. Circulatory collapse is secondary to this anoxemia and responds to treatment of the basic defect. The most important goal, therefore, is correction of anoxia. Measures to stimulate respiration and preserve adequate pulmonary ventilatory function are important. These include artificial respiration as well as coramine and caffeine and perhaps such newer agents as n-allyl normorphine. These alone, however, are insufficient to ensure adequate respiratory gas exchange. Intensive and continuous oxygen therapy is necessary. Oxygen, which should be given by face mask and preferably under positive pressure, is often necessary even after a normal respiratory rate is established. The phenomenon of respiratory depression from removal of the stimulus of anoxemia[5] is not observed. Other measures, such as gastric lavage, preservation of a pharyngeal airway, maintenance of body temperature, prevention of aspiration, change in position and prophylactic chemotherapy, are valuable adjuncts. Despite the presence of pulmonary edema the careful intravenous administration of fluids as necessary has been without ill effect (1 or 2 liters at less than 12 cc. a minute).

Acute opium intoxication with pulmonary edema may present a problem in diagnosis because of the occasional occurrence of tenacious bloody sputum. One of the early patients was admitted to the hospital with a story of sudden collapse. Shortly after admission he became febrile and began to raise thick, bloody sputum. On the basis of the history and initial chest roentgenogram showing abnormal areas of density, a preliminary diagnosis of acute pneumonia due to Friedländer's bacillus (*Klebsiella pneumoniae*) was made. However, the patient's subsequent course and additional information established a diagnosis of acute opium intoxication with pulmonary edema.

Summary and Conclusions

The medical emergency of acute opium intoxication is likely to be more frequently encountered. It is seen in both the addict and the nonaddict. The diagnosis should be strongly suggested by the triad of coma, pinpoint pupils and greatly depressed respirations. Except for occasional bloody sputum there is little to cause one to suspect the frequent occurrence of pulmonary edema, which is nevertheless most important in the pathophysiology of acute opium intoxication because it interposes a barrier to respiratory gas exchange and thus accentuates the depression of the respiratory center caused by the opiate. Intensive and prolonged oxygen therapy is therefore necessary and is remarkably effective in the treatment of even apparently moribund patients.

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THE MASSACHUSETTS REHABILITATION COMMISSION (MEDICAL), DEPARTMENT OF INDUSTRIAL ACCIDENTS

Its Duties and Activities

Jacob L. Rudd, M.D.*

BOSTON

An explanation of the part that the Massachusetts Rehabilitation Commission plays in the Department of Industrial Accidents requires a brief outline of the workings of the Industrial Accident Board itself.

Industrial Accident Board

In 1911 the General Court of the Commonwealth enacted into law the Massachusetts Workmen's Compensation Act. The Act became effective in 1912 and since then has proved to be one of the most successful legal reforms in Massachusetts.

Previously, the victims of industrial accidents found themselves entrapped in a maze of legal entanglements. If they wished to claim damage for their injuries, their only recourse was to the civil courts, where they were confronted with costly delays and cumbersome procedures. If an employee sustains an injury "arising out of and in the course of his employment" he is now awarded weekly compensation based on his average weekly wage, payment of which is to continue, in most cases, for the duration of his disability. Such an injured employee is allowed medical expenses and his dependents are protected should his injury result in death. The job of administering the law was given, in 1912, to a newly created agency, the Industrial Accident Board. This board, a quasi-judicial body, was given exclusive jurisdiction in determining any issues that might arise between the employee and the employer.

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An insight into the importance of the work of the Industrial Accident Board may be gleaned from a few statistics. Last year 280,000 cases were reported, of which 58,000 were "lost-time" accidents. In these 58,000 cases 23,000 persons lost less than seven calendar days of work, so that no compensation was paid. That left a total of 35,000 cases "brought under agreement" — that is, for which compensation was paid. Among these 35,000 cases there were 217 deaths, 31 employees were permanently and totally incapacitated, and 1085 suffered permanent partial incapacity.

On the financial side of the ledger approximately $22,000,000 was paid, under the Act, by the insurers for compensation, medical care, dependency and specific loss.

Massachusetts Rehabilitation Commission

On August 16, 1950, General Laws, Chapter 152 (Workmen's Compensation), were amended. The General Court of 1950 enacted Chapter 767, establishing a rehabilitation commission in the Department of Industrial Accidents, Commonwealth of Massachusetts, and prescribing its duties relative to the problems of the rehabilitation of seriously injured industrial workers. The Commission is a 7-man board, consisting of the chairman of the Industrial Accident Board and the Commissioner of Education as *ex-officio* members who may designate a member of their departments to represent them on the Commission. The rest of the membership includes a registered physician, a physiatrist; an employee; a representative of a casualty insurance company; an employer; and a person who has undergone a rehabilitation training program.

On April 4, 1951, a letter requesting co-operation was sent to all insurance companies writing Workmen's Compensation Insurance, to all hospital administrators and to managers of rehabilitation centers in Massachusetts, inviting them to record with the Rehabilitation Commission any pertinent information that would help the Commissioners determine whether they were operating a rehabilitation facility qualified (according to the new law) to furnish complete services for all types of disablement.

The letter, quoting portions of the new Chapter, read as follows:

> Section 30A. The rehabilitation commission established under Section ten of Chapter twenty-four shall continuously study the problems of rehabilitation and shall examine such rehabilitation facilities, both private and public, and establish a list of physicians available to render competent rehabilitation services for seriously injured industrial workers. Rehabilitation facilities shall include all medical, surgical, hospital, prosthesis, vocational, educational and physical restoration services. No facility shall be considered as qualified unless it is established to provide rehabilitation services for persons suffering from some specialized or general type of disablement within the field of industrial injury and unless such facility is operated under the supervision of physicians qualified to render rehabilitation services; is staffed with trained and qualified technicians and has received a certificate of qualification from the said commission. No physician shall be considered as qualified unless he has had experience for a reasonable term of years in a qualified rehabilitation facility or is qualified for a special rehabilitation procedure because he holds a certification by an American Board of Specialty.
>
> Section 30B. The Rehabilitation Commission shall designate to act as impartial rehabilitation examiners, physicians who are specifically qualified and experienced in special means and methods of rehabilitation. The chairman of the Industrial Accident Board shall appoint such physicians as are so designated by said commission to serve as impartial rehabilitation examiners and to assist the department and the commission in cases which may require rehabilitation services.
>
> An insurer or self-insurer shall furnish rehabilitation services by a rehabilitation facility or by a physician who, in the opinion of the commission, is qualified to render rehabilitation services. Fees for rehabilitation services shall be the reasonable and necessary cost of such services; expenses for the rehabilitation of the injured employee shall include travel, board and room when necessary, subject to the approval of the department, and shall be paid for by the insurer.

The letter concluded:

> The newly established commission must determine as soon as possible what rehabilitation facilities are now available, together with the names and qualifications of professional personnel staffing them. Rehabilitation hospitals, and insurance companies writing Workmen's Compensation in Massachusetts are earnestly requested to forward this essential information at their early convenience to the Rehabilitation Commission in the Department of Industrial Accidents, Room 272, State House, Boston, Massachusetts.

Numerous replies were received, and the following organizations were officially inspected, approved and subsequently presented with certificates: Liberty Mutual Rehabilitation Center, Boston; Department of Medical Rehabilitation of the Boston Dispensary (a unit of the New England Medical Center); Bay State Medical Rehabilitation Center, Boston (at the Massachusetts General Hospital); Sol-E-Mar Hospital, South Dartmouth, Massachusetts (a unit of St. Luke's Hospital, New Bedford); American Mutual Rehabilitation Clinic, Boston; Department of Physical Medicine and Rehabilitation, Boston City Hospital; Rehabilitation Center of Worcester (Bay State Society for the Crippled and Handicapped, Incorporated); and Rehabilitation Center of Western Massachusetts, Springfield (Bay State Society for Crippled and Handicapped, Incorporated).

The certification of facilities required not only travel to visit and evaluate the personnel and equipment but also subsequent meetings, which included discussions concerning the strength, weakness and potentialities of the center under investigation. Upon acceptance of the facility the certification was formally voted, the certificate was duly inscribed, and presentation was made with attendant publicity as desired by the recipient.

If a facility applies for certification and then, when thoroughly investigated, does not meet the stringent requirements of Chapter 767 of the General Laws, it is informed of its lack of equipment or of technically trained personnel. It is also advised regarding the specific steps that should be taken to

meet the legal qualifications. The door is seldom closed to a facility. It is encouraged and counselled to follow the pattern set by other facilities that have been certified, and to bring its clinic up to the standards necessary for the rehabilitation of the seriously injured industrial-accident cases.

Additional Activities

The Commission has been meeting on an average of once a week to handle the cases referred to it by members of insurance companies, the Industrial Accident Board, private physicians and others. Not infrequently, interviews are held with the patient, with the insurance-company representatives or with applicants interested in the certification of a center. At times it is necessary for one or more of the Commissioners to travel to the hospital or to the home of a person severely disabled in an industrial accident. At the request of the insurance companies, a visit was recently made to two veterans, paraplegic patients, who suffered injury in industry, but who were being treated at the Cushing Veterans Administration Hospital.

Patients with amputations who needed instruction regarding the use of prostheses have been seen at the Commission meeting and instructed, when deemed advisable, with the aid of a prosthetist, in the use of hooks or whatever artificial appliances they were wearing.

An insurance company asked the Commission to show a man with a potential amputation, who was reluctant to part with what little was left of a hand, how well a prosthesis could serve him after he learned to use it. Two skilled prosthetists (one, a member of the Commission) demonstrated their technic with the hooks when the man and his wife arrived to see the possibilities in a prosthesis worn by men trained in its use.

One of the Commissioners, an executive of a casualty insurance company, is sometimes called on for insurance advice by the disabled industrial worker at some of the meetings. The chairman of the Industrial Accident Board, who is a commissioner, *ex-officio*, is often asked for information about the probable action of his board regarding a particular case. The representative of the Commissioner of Education, the director of the Division of Vocational Rehabilitation, presents what educational and vocational help is required. He makes the necessary appointments for the disabled applicant, so that testing, guidance, counseling and placement may be effected. The Rehabilitation Commission is striving to increase the quality as well as the quantity of jobs for the rehabilitated.

How Cases are Handled

As an illustration of the disposition made of most of the patients, a seriously injured industrial worker may be referred to any of the following:

A rehabilitation specialist selected by the Commission as the expert who could throw the needed additional light on a difficult problem.

A panel of 3 or 4 specialists in a hospital conference — an abbreviated Veterans Administration hospital conference. Usually, an orthopedist, a neurosurgeon, and a general practitioner participate in this conference, depending upon and varying with the type of case referred.

The director of the Division of Vocational Rehabilitation for training, if needed, and the speedy return to some sort of employment. This is a frequent method of referral.

A certified rehabilitation facility such as the Bay State Medical Rehabilitation Center or the New England Medical Center, where physical medicine and rehabilitation services may be administered.

At present the outstanding need is for a center housing a huge factory. It should contain a variety of types of mechanical equipment for conducting prevocational tests and for training or retraining the rehabilitated person in job operations. It should also be used for those who are through with their rehabilitation but have not yet been able to obtain suitable employment. This will help them return to industry or to do a type of work for which they have been tested and for which they are known to be physically capable. This is the kind of workshop required to help bridge that sometimes wide gap between "rehabilitation completed" and "work begun."

The Commission is now receiving earlier referrals from the Industrial Accident Board and others, but so that needed rehabilitation services can be offered as soon as possible to the seriously injured the insurers are being urged to report these cases as promptly to the Commission as they do to the Industrial Accident Board.

Unusual Activities

Many related but extracurricular activities are performed by the Commission in the medical aspects of rehabilitation.

When the Massachusetts Chapter of the American Physical Therapy Association applied for licensure in Massachusetts, the Rehabilitation Commission volunteered its services to help out where possible in the legislature, even to the extent of having a representative appear at the legislative hearings and formally stating that the Commission was in favor of the request of the physical therapists.

When the Corrective Therapists applied for licensure the Rehabilitation Commission considered it its duty to participate actively in a project that it believed advantageous for rehabilitation in the Commonwealth. The Commission believed that it should know who in hospitals, in rehabilitation centers, in private practice, or with private physi-

cians were qualified as rehabilitation technicians (whatever the field of rehabilitation) and, of equal importance, those who were not qualified.

Changes Wrought by "Baby Hoover Commission"

When the Commission thought that it had begun to function fairly smoothly and effectively in the Department of Industrial Accidents, the Special Commission on the Structure of State Government — popularly known as the "Baby Hoover Commission" — submitted as one of its recommendations, the incorporation of the Rehabilitation Commission into the Department of Education.

The chairman of the Rehabilitation Commission, with the executive secretary and the representative of the General Court (who had originally sponsored the Act creating the Commission), appeared before the Baby Hoover Commission. In an extremely interesting session, a number of points were clarified.

On July 4, 1952, the General Court passed Chapter 630, which is "An Act relative to the organization, Powers and Duties of the State Board for Vocational Education." This Act became law on October 5, 1952.

In brief, this new legislation broadens materially the duties of the Rehabilitation Commission. Basically, the Commission is given increasing responsibility as it becomes a part of the newly created "State Board of Vocational Education," in the Department of Education.

The original Rehabilitation Commission remains intact, however, and becomes a subcommittee known as the "Massachusetts Rehabilitation Commission." In other words, the Rehabilitation Commission takes on additional powers and duties, including the rehabilitation of some of the injured and the handicapped employable people not involved in industrial accidents. It must also participate more actively in the entire educational, vocational and medical rehabilitation program for the Commonwealth.

Judging by the statements of members of the "Baby Hoover Commission" the new law is a recognition of satisfactory accomplishments by the Rehabilitation Commission. It was placed in the Department of Education in an attempt to utilize its services in this additional sphere.

If the new law assists the Massachusetts Rehabilitation Commission in attaining the objectives established by its originators, an earlier return of injured workers to the community and to productivity as self-respecting, self-supporting citizens, the additional burdens will be light.

371 Commonwealth Avenue

MEDICAL PROGRESS

PHARMACOLOGIC ASPECTS OF ADRENOCORTICAL STEROIDS AND ACTH IN MAN (Continued)*

George W. Thorn, M.D.,† Dalton Jenkins, M.D.,‡ John C. Laidlaw, M.D.,§ Frederick C. Goetz, M.D.,¶ Joseph F. Dingman, M.D.,|| Walter L. Arons, M.D.** David H. P. Streeten, M.R.C.P.,** and Brian H. McCracken, M.D.††

BOSTON

Effect of cortisone on growth: An impressive array of evidence demonstrates that under certain conditions body growth is suppressed by oxygenated corticosteroids[145] or by intensive adrenocortical stimulation with ACTH.[323] Cortisone fails to sustain a normal growth rate in young, immature, adrenalectomized rats[324] and, in large doses, frankly inhibits growth in mature adrenalectomized[325] and normal[209] rats. Furthermore, inhibition may be extreme, despite a greatly increased food intake during cortisone administration. Since high-level cortisone treatment may interfere with growth of epiphyseal cartilage in immature animals, and suppress chondrogenesis and osteogenesis in mature rats,[227] it is not surprising that elevated levels of corticosteroids antagonize the somatotrophic effects of growth hormone.[226] Other structures particularly susceptible to growth retardation are the skin and its appendages, lymphoid organs and mesenchymal tissue.[326] The local application of cortisone to these tissues reduces or even halts further growth, suggesting that the hormone exerts a direct cellular action on growth processes in addition to an indirect effect consequent to the induction of a negative nitrogen balance.[227] Indeed, a suppression of mitotic activity in the skin epithelium of mice followed both parenteral and local administration of cortisone acetate.[327] DeRopp[328] has shown that

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the capacity of the hormone to suppress growth extends even to certain plant tumors. That growth inhibition is of more than academic interest, however, is indicated by reports of a suppression of growth in children with Cushing's syndrome,[329] in premature infants during intensive ACTH therapy[330] and in infants with congenital adrenal hyperplasia during treatment with cortisone.[331]

Of particular interest are the numerous studies establishing the capacity of cortisone to inhibit, at least temporarily, the growth of certain tumors. Neoplasms demonstrated to be susceptible to suppression include transplantable lymphosarcomas in mice,[332] skin carcinomas induced in mice by methylcholanthrene,[333] the Walker carcinoma in rats,[334] transplanted rhabdomyosarcomas in mice[335] and osteogenic sarcomas of mice.[336] In almost all cases tumors eventually recurred and became refractory to further treatment. In man cortisone has produced regression of lymphomatous tumors, including lymphosarcoma, leukemia, Hodgkin's disease and, in occasional cases, plasma-cell myeloma.[148] Unfortunately, the neoplastic process recurs when treatment is withdrawn, and response to further therapy is usually diminished or lacking. Furthermore, therapeutic results after cortisone administration, even in these relatively susceptible forms of tumor, are unpredictable. This implies a peculiar therapeutic specificity that has been interpreted as evidence for the existence of multiple etiologic factors. Hence it is possible that the results of steroid therapy are largely determined by both the intrinsic biologic nature of the cells affected and the metabolic alterations produced in the environment of those cells, rather than by an effect on neoplastic growth in general.[337]

The administration of large doses of cortisone to pregnant mice has been found to result in a surprisingly high incidence of cleft palate in the offspring.[338] In view of the fact that the defect could be produced after the period when the nasomaxillary fissure normally closes, the authors suggested that the defect was degenerative rather than a consequence of delayed development. In view of the comparatively immense doses of hormone used, it is not possible to transfer the implications of these experiments to the therapeutic use of cortisone in human pregnancy.[339] Nevertheless, the data are of great interest in relation to the problem of etiologic factors in the development of congenital defects.

Effects on mechanisms of defense: The capacity of the organism to respond to stress is profoundly modified in the presence of a deficiency or excess of adrenocortical hormones. Vulnerability to exogenous stress is the predominant characteristic of patients with Addison's disease; equally striking is the marked protection from ordinary levels of stress that relatively small quantities of 11, 17-oxysteroids such as cortisone afford. These stable doses of hormone do not, however, permit the flexibility of response to varying grades of stress enjoyed by the person with intact adrenal glands. Indeed, this mobilization of adrenocortical steroids in response to exogenous stress forms the basis of Selye's challenging concept of the processes of adaptation.[275] This concept, embracing the sum of the systemic reactions of the body that follow exposure to stress, has succeeded in emphasizing the central role of pituitary-adrenal activation in the mechanisms of nonspecific resistance. Continuous overactivity of this system (Cushing's disease), however, may profoundly alter the reactions of the organism to certain forms of stress, particularly infection and trauma, indicating a potent influence of adrenal steroids on processes of inflammation and the reparative capacity of the mesenchymal system. That a state of induced hyperadrenocorticism may likewise influence these processes has become increasingly evident in this era of extensive investigation of the experimental and therapeutic applications of adrenocortical hormones.

The original observations of Hench et al.[102] on the dramatic effect of cortisone and ACTH on rheumatoid arthritis served to call attention to the capacity of adrenocortical steroids to suppress the processes of inflammation. This suppression was evidenced clinically by a rapid lessening of the classic signs of inflammation and histologically by a decreased number of plasma cells and lymphocytes, a reduction of papillary tufting, a decreased deposition of fibrin and diminution of necrosis and edema in the synovial membrane. These historic observations have been confirmed in numerous studies in which cortisone has been shown to be capable of suppressing the inflammatory response to a wide variety of inciting agents, including chemical irritants,[340, 341] foreign protein[342, 343] and microorganisms.[344, 345]

In a detailed study of the tissue response to the subcutaneous injection of histamine in adrenalectomized mice, Dougherty[346] found the intensity of inflammatory reaction to be reciprocally proportional to the amount of cortisone or hydrocortisone available in the inflamed area. The hormones effectively inhibited the destruction of fibroblasts, and the invasion of polymorphonuclear leukocytes and macrophages. Rebuck et al.,[347] employing the skin-window technic in man, studied the effect of adrenocortical stimulation on the inflammatory reaction to foreign proteins (ovalbumin and tuberculin). As a consequence of hormone therapy there was an inhibition of lymphocytic hypertrophy and migration resulting in a relative predominance of neutrophils and histiocytes. The effect of intramuscularly injected cortisone on the local inflammatory response to cutaneous and testicular pneumococcal infections in rabbits has been described by Germuth and his associates.[348] In control animals there were numerous neutro-

philic leukocytes, necrosis and thrombosis of small vessels, hemorrhage and edema. In treated animals the leukocytic response was definitely suppressed, the blood vessels were normal, and the number of viable bacteria was greatly increased. Since the number of circulating neutrophils increased, the paucity of these cells at the inflammatory site was considered to be the consequence of an interference with cellular migration. The capacity of the inflammatory process to limit the spread of infection was clearly diminished during cortisone administration, and an intensification of bacteremia occurred. In view of the possible production of hyaluronic acid by mast cells, it is of interest that in several species, including man, the number of these cells in cutaneous connective tissue declined during the administration of cortisone.[349]

The studies of Ebert and Barclay,[350] utilizing the ear-window technic in rabbits, have emphasized the changes produced by parenterally administered cortisone on the vascular component of the focal inflammatory response to tuberculin. In untreated animals the reaction was associated with an increased sticking of leukocytes to vascular endothelium, lability of the circulation evidenced by alternating periods of vasoconstriction and dilatation, hemoconcentration, stasis and vascular thrombosis, and increased exudation and liquefaction of caseous material. The effective suppression of these changes by cortisone was considered to be the result of a preservation of vascular "tone" and endothelium. Menkin[351] has also demonstrated, by dye-diffusion studies, a reversal of the enhanced capillary permeability associated with acute inflammation.

It is clear, therefore, that cortisone exerts a suppressive effect on the basic processes of inflammation. Vascular permeability is decreased, exudation diminished, and the migration of inflammatory cells materially impaired, resulting in an over-all reduction in local phagocytic activity. Consequently, the classic signs of acute inflammation are lessened, and the spread of micro-organisms facilitated. Furthermore, reparative process may be inhibited by virtue of the potent effects on the reactivity of other mesenchymal elements. Cortisone affects all components of connective tissue, resulting in a decrease of fibroplasia and a shrinkage of collagenous fibers. These changes are reflected in delayed wound healing. Intensification of hormone activity leads to a disorganization of the reticulum and probably results in an inhibition of heteroplastic differentiation of lymphocytes[352] and a curtailed production from parent reticulum of all types of phagocytic cells.[235]

The inhibitory effects of cortisone on the manifestations of infectious and inflammatory disease are not confined to the local processes of inflammation. The systemic manifestations, such as fever and signs of toxemia, may also be suppressed. This apparently beneficial alteration in the reaction of the host is illusory, however, because the etiologic agent remains unaffected by the hormone. The now classic example of this phenomenon is the striking but temporary suppression of the manifestations of rheumatoid arthritis. The perforation of a viscus without signs of peritonitis and the dissemination of infection without signs of septicemia are extreme, and potentially dangerous, examples of the same phenomenon. The exacerbation of tuberculosis during cortisone administration deserves special emphasis. Numerous reports on the aggravation of experimental tuberculous infection in animals have appeared,[353] and a growing clinical experience has confirmed these observations in man.[354] It is strongly recommended, therefore, that cortisone and ACTH should not be used in patients with active tuberculosis and should be employed only with considerable caution in patients with latent or inactive disease.

The dramatic effects of cortisone and ACTH on diseases known or assumed to be of allergic origin have stimulated extensive investigation of the influence of these hormones on the humoral mechanisms of defense. An extensive literature has appeared that is highly complex, often conflicting and difficult to interpret. Recently, however, certain trends have emerged, based on meticulous, well controlled studies, which promise eventual clarification.

The report of Dougherty, Chase and White,[355] in 1945, called attention to the possible relation between adrenal hormones and antibody formation. Evidence was presented that the administration of ACTH to immunized rabbits resulted in a liberation of antibodies from lymphoid tissue. Subsequent workers, however,[356, 357] were unable to detect a significant rise in antibody titer under these conditions. In addition, numerous studies in man failed to demonstrate an effect of cortisone on circulating antibody titers[240, 358] or on the production of antibodies in response to specific sensitization.[359] However, more recent experimental studies in animals employing careful quantitative immunologic technics have indicated that these hormones are not without effect on serum antibody levels. Bjørneboe et al.[360] and Germuth[361] have demonstrated a significant inhibition of the rise in antibody titers following specific sensitization during the administration of cortisone and ACTH. Moreover, the hormones failed to alter the rate of disappearance of antibody in passively immunized animals. It was concluded that the predominant effect of ACTH and cortisone was an inhibition of antibody synthesis. The observations by Germuth and his co-workers[361] of a marked suppression of the *active* Arthus phenomenon during hormone administration and the failure of Fischel[362] to inhibit the local *passive* Arthus reaction are consistent with this view. On the other hand, the occasional ob-

servations of a marked decline in antibody level after only a few hours of ACTH or cortisone administration[363] indicate, in view of a demonstrated half life of antibody protein of approximately fourteen days,[364] that an alteration in distribution or acceleration of antibody degradation may also be involved.

It is generally considered that cortisone is incapable of inhibiting the union of antigen and antibody. This view is based on the failure of most workers to prevent anaphylaxis in various species. In addition, it has been observed that cortisone may block actively induced nephrotoxic nephritis (bovine gamma globulin,[365] and horse serum[186]), whereas the passively induced disease (kidney antiserum) is not prevented.[277] In the former an interference with antibody production undoubtedly occurs,[366] but a suppression of tissue reactivity by the hormone may also be involved.[367] It should be pointed out that in a few experiments[368, 369] acute anaphylaxis has been successfully prevented. This has occurred with comparatively large doses of the hormone, and it has been assumed that a block in tissue response is involved.[346]

The resemblance between the pharmacologic effects of histamine and the manifestations of acute anaphylaxis has led to the suggestion that antigen-antibody union may provoke a release of histamine or histamine-like substances[370] from the tissues. A number of studies indicate that intense adrenocortical stimulation does not significantly alter the ability of tissue to release histamine-like substances or to respond to either these substances or histamine itself.[371] It is unlikely, therefore, that the therapeutic effectiveness of cortisone in allergic states is related to an interference with these mechanisms.

The effects of cortisone and ACTH on certain local allergic phenomena have also been investigated. An inhibition of the tuberculin reaction by comparatively large doses of the hormones has been reported by Long and Favour,[372] Stoerk[373] and others. Kabat[374] has observed a suppression of allergic encephalomyelitis in animals. It is generally agreed that the Shwartzman reaction may also be effectively blocked.[375] It appears that the effects of the hormones in these phenomena depend on an interference with some phase of tissue reactivity.

There is no doubt that cortisone and ACTH may favorably modify the course of a variety of diseases of hypersensitivity in man, such as allergic dermatitis,[376] bronchial asthma[377] and hay fever.[378] The actual site of action is not clearly understood. Fischel[366] has recently discussed with admirable clarity the potential implications of the experimental observations cited above to the mode of action of these hormones in human allergic disorders. It was emphasized that although it has been clearly demonstrated that antibody synthesis is depressed by cortisone, the depression is small in extent and occurs only when extraordinarily large quantities of the hormones are employed. That the antibody effect is probably not of major importance in the therapy of allergic states is evident in patients with asthma or hay fever, whose symptoms may be adequately controlled by cortisone but in whom sufficient reagin or antibody is present to give satisfactory skin reactions. Fischel concludes that the clinical efficacy of cortisone probably bears little relation to antibody inhibition except in certain specific disorders such as acquired hemolytic anemia, in which clinical improvement usually coincides with a disappearance of abnormal antibodies from the blood.

In summary, it is apparent that cortisone and ACTH are capable of suppressing the local and systemic response of the organism to a wide variety of inciting agents. It is probable that the mechanism of action of these hormones on the hypersensitive state is fundamentally similar to their effect on the inflammatory response of connective tissue. In all likelihood the common factor in the multiple actions of cortisone and ACTH on the bodily mechanisms of defense is a modification of the reactivity of mesenchymal tissue.

Toxicity. Cortisone is either a natural secretory product of the adrenal cortex or a potent, metabolically active adrenal-steroid derivative. It is to be expected, therefore, that the undesirable effects that may follow its clinical use would be of two general types: those due to overdosage of the hormone, representing an exaggeration of its physiologic actions and occurring during intensive and prolonged administration; and those occurring chiefly after hormone withdrawal, reflecting a state of adrenal insufficiency induced by hormonal suppression of adrenocortical function. The former effects are epitomized in the patient with classic Cushing's syndrome; the latter exemplify the major metabolic defects of patients with Addison's disease.

It is to be emphasized that the dose of cortisone ordinarily employed in nonspecific clinical therapy is different from the quantity of hormone normally secreted by the adrenal cortex. Although it has been suggested that the therapeutic action of cortisone may depend upon the correction of a state of relative adrenal-hormone deficiency at the local site of disease, there is no doubt that to achieve a therapeutic effect one must definitely exceed the well delineated dosage of cortisone required in the maintenance therapy of patients with adrenal insufficiency. Indeed, the very basis of successful steroid therapy appears to be the controlled induction of a state of hormone overdosage. Thus, it is inevitable that effective cortisone therapy will be associated with significant alterations in the normal pattern of metabolic reactions. Initially, these alterations are effectively offset by the compensatory mechanisms of homeostasis. With continuing hormonal therapy, however, the capacity

of these mechanisms may be exceeded, and overt manifestations of overdosage may appear, at first on a biochemical plane and eventually on a structural level. It should be pointed out that certain conditions predispose to the development of specific overdosage phenomena at dosage levels that are incapable of inducing the entire picture of Cushing's syndrome. Pertinent examples include the production of frank diabetes in patients with latent diabetes, the exacerbation of a quiescent peptic ulcer, the aggravation of hypertension in the presence of renal damage and the development of osteoporosis in immobilized patients. Both the biochemical and the structural changes associated with prolonged cortisone administration have been discussed in detail in the earlier section on physiologic actions. Fortunately, the majority of these changes can be prevented or minimized by specific measures and, with few exceptions, they completely disappear after discontinuation of therapy.

In contrast to the manifestations of hormone excess that appear *during* cortisone administration, symptoms of hormone deficiency occur with either a drastic reduction in dosage or the abrupt cessation of the drug. These symptoms may be mild or severe, depending on the duration of therapy, level of dosage and rapidity of hormone withdrawal. After prolonged treatment, even with moderate doses of cortisone, a profound depression of adrenocortical function may ensue. In some patients the clinical manifestations of adrenal insufficiency may continue for a protracted period; in unusual cases this state may persist for as long as sixty to ninety days. The advent of adrenal insufficiency, particularly if it is accompanied by either a violent relapse of the disease for which hormonal therapy was instituted or by an intercurrent stress (such as infection or trauma), may prove disastrous. Fortunately, serious manifestations of adrenocortical insufficiency associated with cortisone withdrawal may be minimized by a gradual tapering of hormone dosage and the concomitant stimulation of the adrenal gland with ACTH.

In addition to the precipitation of adrenocortical insufficiency by the sudden cessation of cortisone therapy, a state of relative hypoadrenocorticism may develop during the course of therapy as a consequence of superimposed stress. Under these circumstances, it is assumed that the adrenocortical atrophy secondary to long-continued therapy prevents or modifies the capacity of the gland to increase its secretion of hormone. The susceptibility of patients to superimposed stress in the presence of what would ordinarily be an adequate quantity of circulating hormone is no doubt conditioned by the adaptation of the organism to the continued administration of high doses of hormone. A state of relative adrenal insufficiency after the sudden imposition of stress may even occur in a patient who, because of prolonged cortisone therapy, exhibits the clinical manifestations of Cushing's syndrome. In these circumstances additional cortisone should be given.

Certain procedures should be carried out in all patients who are candidates for *prolonged* cortisone therapy. In the first place, in view of the potential aggravation of active tuberculosis by cortisone, x-ray examination of the lungs is advised. In the presence of active tuberculous disease, treatment with cortisone acetate should be withheld except as substitution therapy in patients with Addison's disease. Should inactive lesions be discovered, hormone therapy may be instituted, but periodic re-examinations are indicated. Secondly, a history suggestive of peptic ulcer warrants roentgenologic examination of the upper gastrointestinal tract. In the presence of an active ulcer, the administration of cortisone is contraindicated. If a deformity indicative of a healed lesion is discovered, hormone therapy may only be undertaken if the indications for its use are carefully evaluated and accepted measures for ulcer management are instituted. Thirdly, a urinalysis for the presence of glucose should be performed. In the presence of a strong family history of diabetes both a fasting and a postprandial blood sugar determination should be made. Neither latent nor overt diabetes mellitus contraindicates cortisone therapy. However, in their presence periodic blood sugar measurements and routine urine tests are indicated. Finally, the basal blood pressure should be determined. An elevated level, even in the presence of renal disease, does not prohibit the therapeutic use of cortisone, but does indicate the necessity for frequent blood-pressure measurements throughout therapy.

The use of cortisone in patients with heart disease is a problem requiring careful medical judgement in individual cases. Neither severe though well compensated cardiac disease nor heart failure that is satisfactorily controlled by medical therapy contraindicates treatment with the hormone; in these cases, however, one must take particular care to prevent either excessive sodium and water retention or potassium loss. Intractable heart failure is a contraindication to cortisone therapy unless it is due to a condition that may be alleviated by the hormone — for example, acute rheumatic carditis.

A low-salt diet and supplementary potassium administration are routine measures that should always accompany prolonged cortisone treatment. Sodium restriction minimizes, but does not entirely eliminate, urinary potassium loss[15, 279] in a manner comparable to that described for desoxycorticosterone. A high potassium intake, on the other hand, materially reduces sodium retention.[380] These measures, therefore, will largely offset the development of edema due to sodium and water retention and the muscular weakness and hypokaliemic alkalosis caused by potassium depletion. A few relatively simple measures facilitate the detection of

the common manifestations of overdosage.[381] Body weight should be determined daily. If weight gain and edema ensue, rigorous salt restriction should be instituted, and, if necessary, diuretic agents should be administered. Potassium depletion may be evidenced by skeletal-muscle weakness, characteristic electrocardiographic changes, an increase in serum carbon dioxide combining power and a decrease in serum chloride and potassium levels (hypokaliemic alkalosis). The development of significant potassium depletion, however, is unusual in the presence of an adequate diet and a daily supplement of 1 to 3 gm. of a potassium salt. Periodic urinalyses for the presence of glucose should be performed. Glycosuria in the absence of a significant degree of hyperglycemia may be ignored. If a marked degree of hyperglycemia develops, insulin therapy should be instituted.

The remaining common complications of cortisone therapy can be detected by careful clinical observation; rounding of the face is a sensitive and early sign of overdosage. Characteristic changes in fat distribution, as seen in Cushing's syndrome, likewise may occur relatively early. Acne, mild hirsutism and eventually cutaneous striae may appear. A suppression of menses and changes in libido are not infrequent. These manifestations do not contraindicate continued hormone therapy.

The major complications of intensive cortisone therapy are few, but of serious import. The development of symptoms and signs of peptic ulceration constitutes an absolute contraindication to the continuation of therapy, owing to the danger of perforation and massive hemorrhage. One should be constantly alert for the development of intercurrent infection since steroid therapy may effectively attenuate the inflammatory manifestations of infection without affecting the etiologic agent. If the causative organism is known and an effective antibiotic is available, hormone therapy need not be discontinued. On the other hand, if effective control of the infectious agent is not possible, continuation of cortisone therapy may prove extremely hazardous. One must be particularly alert for the development of a severe degree of osteoporosis, with its attendant hazard of pathologic fracture, in patients long immobilized or in whom osteoporosis already exists (as in postmenopausal women). In these cases the maintenance of a high-protein intake and the administration of testosterone may at least partially counteract the antianabolic effects of cortisone. A serious interference with wound healing rarely occurs unless the dosage is high — that is, greater than 150 mg. a day — and prolonged, and protein intake is inadequate. A growing experience indicates that the vast majority of fractures, traumatic wounds and operative incisions heal satisfactorily despite concomitant cortisone administration. An increasing number of reports suggest that an increased incidence of thromboembolic phenomena may be associated with cortisone therapy, particularly during the period immediately after withdrawal. It appears that the presence of chronic liver disease may predispose to the development of this complication. Rarely, signs of vascular fragility, such as easy bruisability and purpura, may become severe enough to require a reduction in dosage. Convulsive seizures occasionally occur, being seen predominantly in patients with disorders of the central nervous system. In these cases either a reduction of the dose or institution of anticonvulsant therapy is indicated.

In the present state of knowledge it appears impossible to predict accurately which patients may manifest severe mental symptoms during cortisone therapy. Mild euphoria or, less commonly, mild depression and moderate mental and physical hyperactivity do not in themselves necessitate discontinuation of therapy. A marked progression of these symptoms or the appearance of certain warning signs, such as pronounced frontal paresthesias, uncontrolled thoughts and mental confusion, may presage the development of serious aberrations of affect or behavior and require immediate cessation of treatment.

The need for meticulous care in withdrawal of cortisone after prolonged therapy has already been emphasized. Dosage should be tapered off gradually (for example, 12.5 to 25 mg. a day at intervals of two to seven days), especially if the hormone has been given by the oral route. During the period of withdrawal, ACTH should be administered until normal levels of endogenous adrenocortical secretion are restored. Either the intravenous infusion of ACTH or the intramuscular injection of a potent long-acting preparation of ACTH is particularly effective.

Absorption, intermediary metabolism and excretion. Absorption: One of the earliest indications that adrenocortical hormones might be absorbed from the gastrointestinal tract came from a report by Osler[382] in 1896 of a patient with Addison's disease who appeared to improve after the oral administration of a glycerol extract of hog adrenal glands. Many years later, in 1931, Britton and Silvette[383] clearly demonstrated that orally administered adrenocortical extract could serve as adequate substitution therapy in adrenalectomized cats. That cortisone itself might be absorbed from the gastrointestinal tract was first indicated by Freyberg,[384] who reported the effectiveness of oral administration of this hormone in the treatment of rheumatic disease. This view was amply confirmed in many reports describing the oral use of cortisone in a variety of conditions and by the metabolic studies of Thorn et al.[250] in man. Thorn and his associates compared the effects of cortisone given by the oral and intramuscular routes on the circulating eosinophils, urinary sodium, potassium and chloride excretion and thyroid and adrenocortical activity. It was

found that orally administered cortisone reproduced the complete spectrum of metabolic actions of intramuscularly administered cortisone. Its action, however, was more rapid and evanescent. It thus appears that the hormone is rapidly absorbed from the gastrointestinal tract, whereas absorption from an intramuscular depot is slow and prolonged. A further illustration of the different rates of absorption of orally and intramuscularly given cortisone has come from studies of the levels of plasma 17-hydroxycorticosteroids after the administration of the hormone by the two routes. Nelson et al.[386] observed that the oral administration of 200 mg. of cortisone, as either the acetate or the free alcohol, led to a prompt rise in plasma 17-hydroxycorticosteroids, with a peak at approximately one hour and a gradual return to control levels in four to eight hours. A similar response was seen when the free alcohol was given in ethanolic solution by a single intramuscular injection. When 200 mg. of cortisone acetate was administered intramuscularly in saline solution, however, little or no elevation of plasma 17-hydroxycorticosteroid levels occurred.

The pathway of absorption of cortisone from the gastrointestinal tract is unknown. The findings of Chaikoff et al.[386] that in the rat cholesterol is absorbed almost exclusively via the intestinal lymphatics and thence travels through the thoracic lymph duct to the systemic circulation suggest that it may not be correct to assume that the bulk of cortisone that has been absorbed from the intestine passes via the portal vein to the liver.

Intermediary metabolism: No studies of the distribution of administered cortisone in the mammalian organism have been reported. Studies of this kind depend on the availability of isotope-labeled hormone. At present the synthesis of C^{14}-labeled cortisone is being actively pursued, and the results of metabolic studies with this material are eagerly awaited.

Cortisone was first isolated in 1936 from adrenocortical extracts.[70, 92, 93] Subsequently the hormone has been isolated from incubated hog adrenal brei[387] and has been detected by means of paper-partition chromatography in beef adrenal extracts[388] and in perfusates from beef adrenal glands treated with ACTH.[4] The biosynthesis of cortisone from acetate has been demonstrated in hog adrenal slices incubated with C^{14} acetate[387] and in beef adrenal glands through which radioactive acetate has been perfused.[4] The hormone has also been isolated from normal human urine.[389, 390] It has not, however, been detected in the adrenal venous blood[391] or the peripheral blood[392] of animals. It is of interest that cortisone has recently been isolated from the human placenta, suggesting that synthesis of the hormone may occur in this organ.[393]

One cannot be certain from these observations that cortisone is a primary secretory product of the mammalian adrenal gland. Indeed, the finding that hydrocortisone (Compound F) is the principal corticoid in adrenal-gland perfusates,[4] adrenal venous blood[391, 394] and peripheral blood[392] has led to the view[395] that cortisone is either a precursor or a metabolite of the principal adrenal product, Compound F.

There is strong evidence that circulating cortisone undergoes rapid removal from the blood stream and inactivation in the tissues. After the intravenous infusion of cortisone in dogs, Nelson et al.[396] observed that 90 per cent of the hormone disappeared from the circulation within ten minutes. Studies of arteriovenous differences in 17-hydroxycorticosteroid levels after the intravenous injection of cortisone revealed a definite transformation of the hormone in liver, but not in muscle or kidney.[397] Hechter[398] likewise reported the rapid disappearance of cortisone perfused through rat liver. Paschkis and his co-workers[399] incubated cortisone with various tissues of the rat and assayed the remaining hormone by the mouse glycogen-deposition method. They found that tissues such as muscle and brain were just as effective as liver in inactivating the hormone. With similar technics Louchart and Jailer[400] demonstrated over 70 per cent transformation of cortisone after a three-hour incubation with mouse liver, kidney and spleen slices; blood, serum and slices of muscle and brain, however, did not appreciably inactivate the hormone. A detailed investigation of the effects of incubation of cortisone with a variety of surviving rat tissues has recently been reported by Schneider and Horstmann.[401] The hormone was added to minces and slices of liver and kidney, to adrenal homogenates and to slices of diaphragm and heart muscle. The metabolism of the steroid was studied with the aid of ultraviolet spectroscopy, paper chromatography and the Porter–Silber[402] and periodate oxidation assays. It was observed that only liver and, to a lesser extent, kidney caused a rapid reduction of the alpha, beta unsaturated ketone grouping in ring A (Fig. 19) and extensive degradation of the side chain at carbon-17. That the liver also plays an important role in the transformation of cortisone to 17-ketosteroids is indicated by the finding of Butt et al.[403] that less administered cortisone was converted to 17-ketosteroids in patients with hepatic disease than in patients without demonstrable liver damage.

Excretion: No studies on the excretion of cortisone or its metabolites in feces have been reported. It is not known whether cortisone may be completely oxidized to water and carbon dioxide, which would then appear in the expired air; only when isotope-labeled hormone becomes available can this question be answered.

The bulk of knowledge concerning the metabolic fate of cortisone has come from studies of steroids in urine, chiefly in man. It is well known that in patients with Addison's disease the administration

of cortisone leads to an increase in the urine of 17–ketosteroids and steroids with an alpha-ketol side chain at carbon–17 (Fig. 19) (formaldehydogenic steroids[404] and reducing corticosteroids[405, 406]). Similar findings are obtained in subjects with intact adrenal glands provided the dose of cortisone is sufficiently high.[116] With smaller doses of the hormone (50 to 100 mg. daily) the administration of cortisone may be followed by a fall in the 17–ketosteroid values, particularly if the initial levels of urinary 17–ketosteroids are normal or high. It is believed that this fall indicates a suppression of

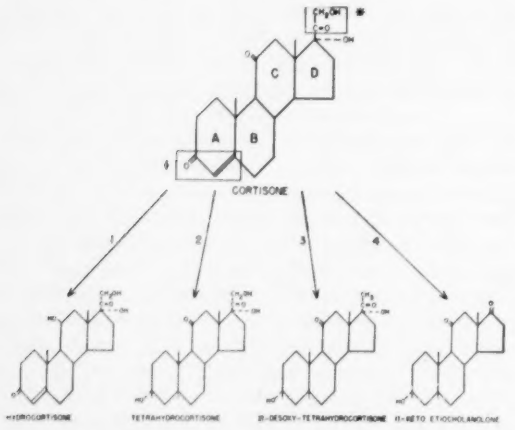

FIGURE 19. *Pathways of Cortisone Metabolism.*
** = Alpha-ketol side chain at carbon-17. † = Alpha, beta unsaturated ketone group in ring A. This figure represents examples of the major metabolic changes that cortisone undergoes in vivo. 1 = Reduction at carbon-11; 2 = reduction of the alpha, beta unsaturated ketone grouping in ring A; the formation of tetrahydrocortisone involves the addition of two hydrogen atoms at carbon-3 and a single hydrogen atom at carbons 4 and 5, with saturation of the 4-5 double bond; 3 = reduction of the alpha, beta unsaturated ketone grouping in ring A, with partial degradation of the side chain at carbon-17; 4 = reduction of the alpha, beta unsaturated ketone group in ring A, with complete degradation of the side chain at carbon-17 and the formation of 17-ketosteroids.*

endogenous adrenocortical secretion and that the 17–ketosteroids excreted during the administration of a "suppressive" dose are derived largely, if not entirely, from the cortisone administered. This belief is supported by the observation that under these conditions the specific 17–ketosteroids, androsterone and etiocholanolone, which are ordinarily found in urine and which, in women, are solely derived from the adrenal cortex, cannot be detected. It should be noted that after the administration of small doses of cortisone to human subjects with intact adrenal glands the magnitude of the rise in urinary 17–ketosteroids and alpha-ketolic corticoids is variable and may not be maintained during long-continued hormone therapy.

The major portion of both the 17–ketosteroids and alpha-ketolic corticoids of normal urine and the urine of human subjects who have been given cortisone appears to be conjugated as glucuronides and ethereal sulfates.[407] A small proportion of these steroids may be conjugated in a manner as yet unknown.[408] The rise in urinary 17–ketosteroids following cortisone administration is largely due to an increased excretion of three 11–oxygenated compounds: 11–keto etiocholanolone, 11, β–hydroxy etiocholanolone and 11, β–hydroxy androsterone.[409-411] There is no discernible increase in the output of steroids such as androsterone, etiocholanolone which lack the C–11 oxygen. Indeed, the loss of the oxygen at carbon–11 during the metabolism of cortisone has not yet been demonstrated. It is believed that the adrenal precursors of the 11–desoxy–17–ketosteroids are hormones that do not initially possess an oxygen atom in the 11 position, such as 11–desoxy–17–hydroxycorticosterone (Compound S) and 17–hydroxyprogesterone. This belief is supported by the demonstration that the administration of the latter substances labeled with radioactive carbon leads to the excretion in the urine of radioactive androsterone and etiocholanolone.[411]

It is well known that the administration of large doses of cortisone in female patients may induce acne and hirsutism. Recent experiments[412] in this laboratory indicate that in man cortisone causes urinary excretion of substances that possess biologic androgen activity. Patients who had undergone bilateral orchidectomy and bilateral complete adrenalectomy for metastatic carcinoma of the prostate were given varying doses of cortisone by mouth, and specimens of urine were assayed for androgenic activity by the chick-comb method. It was observed that, although androgen excretion was proportional to cortisone dosage and roughly paralleled the level of urinary total neutral 17–ketosteroids, even at a dose of 300 mg. a day the level of urinary biologically active androgens was lower than that in a normal man. In addition, the quantity of androgens derived from a given dose of cortisone was somewhat lower than that obtained with hydrocortisone, but higher than that seen with corticosterone.

The principal alpha-ketolic corticoid in normal urine[390, 413] and in the urine of human subjects who have been given cortisone[413] has been identified as tetrahydrocortisone (pregnane-3-alpha,17-alpha,-21-triol-11,20-dione) (Fig. 19). Studies with this compound in man have failed to demonstrate any metabolic activity.[3] Tetrahydro-hydrocortisone (pregnane-3-alpha,11-beta, 17-alpha,21-tetrol-20-one),[411] dihydrocortisone (pregnane-17-alpha,21-diol-3,11-20-trione),[390] cortisone and hydrocortisone[389, 390, 411, 413-415] have also been separated from the alpha-ketolic fraction. The presence of the reduction products — tetrahydrocortisone, tetrahydro-hydrocortisone and dihydrocortisone — indicates that one of the metabolic transformations of cortisone in vivo involves partial or complete saturation of the alpha, beta unsaturated ketone

grouping in ring A. It is interesting that in normal human urine and in the urine of subjects who have received cortisone,[390, 413] the proportion of the urinary tetrahydrocortisone existing as a glucuronide conjugate is much higher than that of the urinary cortisone. These observations suggest that the reduction of cortisone to tetrahydrocortisone facilitates glucuronide conjugation. The possibility that cortisone and hydrocortisone are excreted in part as non-17-hydroxylated alpha ketols must be considered.

That partial transformation of the side chain at carbon-17 may occur during the metabolism of cortisone has been shown by the isolation of 21-desoxy tetrahydrocortisone (pregnane-3-alpha,17-alpha,diol-11,20-dione) from the urine of patients receiving cortisone[411] (Fig. 19). There is also evidence that reduction of the carbon-20 ketone group with production of steroid glycols occurs.[409]

The major metabolic transformations of cortisone in vivo may be summarized as follows: the hormone may be excreted unchanged; it may undergo reduction at carbon-11 with the formation of hydrocortisone (pathway 1, Fig. 19); there may be partial or complete reduction of the alpha,beta unsaturated ketone grouping in ring A, with the formation of dihydrocortisone, tetrahydrocortisone and tetrahydro-hydrocortisone (pathway 2, Fig. 19); partial degradation of the side chain at carbon-17 may occur with the formation of 21-desoxy tetrahydrocortisone (pathway 3, Fig. 19); and there may be complete degradation of the side chain with the formation of 17-ketosteroids (pathway 4, Fig. 19), which appear to retain the oxygen atom at carbon-11. It is to be noted that whereas the reduction of the alpha, beta unsaturated ketone grouping in ring A of cortisone may take place without further catabolism of the steroid, this change must proceed or accompany any metabolic alteration in the side chain at carbon-17.[411] It appears likely that the metabolic products of cortisone are excreted for the most part as conjugates of glucuronic and sulfuric acids. Finally, the need for further development of this complex field is emphasized by the knowledge that the greater part of administered cortisone disappears and is unaccounted for by the sum total of known metabolites.

(To be continued)

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MEDICAL INTELLIGENCE

THE TREATMENT OF URINARY-TRACT INFECTIONS WITH A NEW ANTIBIOTIC — MAGNAMYCIN*

Preliminary Report

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MAGNAMYCIN hydrochloride is a new monobasic antibiotic possessing strong inhibitory activity predominantly against gram-positive bacteria. Preliminary tests on laboratory animals demonstrated that the drug exhibited low toxicity and did not exhibit cross resistance with other antibiotics in general use.¶ In vitro tests showed it to be highly effective against many gram-positive organisms, including enterococci and penicillin-resistant *Micrococcus pyogenes* (var. *aureus*), both of which are becoming increasingly difficult to eradicate.

In this preliminary report, 15 patients with genitourinary infections were selected for treatment with Magnamycin because the majority had failed to respond to other antibiotics, including sulfonamides, penicillin, streptomycin, aureomycin, chloramphenicol and terramycin. Several cases in male patients were complicated by "nonspecific" urethritis or prostatitis, or both. All patients received a complete hematologic and urologic work-up to rule out the presence of obstruction and foreign bodies (calculi). They included the usual renal-function tests, cystoscopy and pyelography as a minimum, with urethroscopy or urethrograms as indicated. Before treatment, urine cultures taken aseptically were submitted to the laboratory for isolation of micro-organisms. Those isolated were tested for sensitivity against several antibiotics, including Magnamycin. Urine was repeatedly checked for sediment, and cultured during the course of Magnamycin therapy. Sensitivity tests were run on all micro-organisms recovered, as a further check on drug resistance as well as a guide for therapy. Magnamycin blood levels were run at periods up to eight hours, and urine levels up to twenty-four hours after three days of therapy.

COURSE OF THERAPY

Most of these patients received 2 gm. of Magnamycin orally (2 capsules four times a day for one week). This dosage was finally selected on the basis of our earlier clinical experience and also on experimental evidence furnished by the manufacturer. Although there was frequent bacteriologic sterility after three days of therapy, Magnamycin was continued for seven days to prevent recurrence. A few patients with chronic urinary infection associated with noncorrectable uropathy were able to remain symptom free for long intervals on a maintenance dose of less than 1 gm. a day.

REACTIONS OR DRUG TOLERANCE

Magnamycin was found generally to be well tolerated in doses adequate for treatment of urinary infections. No serious reactions were encountered (Table 1). In a young male patient on large dosage (3 capsules four times a day) acute colicky abdominal pains, diarrhea and weakness developed, but three days later he was able to tolerate a smaller dosage (1 capsule four times a day) without difficulty. Diarrhea was not noted in patients receiving 1 gm. or less a day, although 2 elderly patients with constipation commented favorably on their regular bowel movements, with soft stools, while on the medication. Some degree of looseness of bowel was observed in nearly all patients receiving 2 gm. a day, but this was never sufficiently severe to interrupt treatment. Some degree of dyspepsia ("gaseous indigestion") and malaise was often noted, reaching its maximum after three days of treatment. No case of pharyngitis, glossitis or hematologic disturbance was seen.

RESPONSE TO THERAPY

In a group of 15 chronic urinary-tract infections for the most part resistant to other antibiotics, 13 showed clinical improvement, with bacteriologic sterility. The remaining 2 patients, who had infections with Magnamycin-resistant organisms did not improve. Time alone will indicate whether the clinical improvement remains permanent. Among the 13 patients who were clinically improved, there were 8 cases of infection with enterococci (7 of *Streptococcus faecalis* and 1 of *Str. zymogenes*), 1 of infection with *M. pyogenes* (var. *aureus*), 1 of infection with *M. pyogenes* (var. *albus*), 1 of infection with the beta-hemolytic streptococcus and 1 case of infection with *Diplococcus pneumoniae*, all showing bacteriologic sterility.

One patient with chronic urethral stricture and a 310 cc. residuum was cleared completely of entero-

*Magnamycin was furnished through the courtesy of Charles Pfizer and Company, Incorporated, Brooklyn, New York — trademark for the new antibiotic carbomycin.

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¶Tanner, F. W., Jr., English, A. R., Lees, T. M., and Routien, J. B. Some properties of Magnamycin: new antibiotic. *Antibiotics & Chemotherapy* 2:441-443, 1952.

coccal infection for four weeks on 3 capsules daily. However, while the patient was still on this regimen, pyuria due to *Escherichia coli* developed, necessitating a change to a sulfonamide—Elkosin.

Repeated bacteriologic examination of urine after initiation of treatment provided a means of comparing clinical improvement with laboratory findings. In general, with the exception cited above, there was good correlation between prognosis based on laboratory findings and actual response. Blood and urinary levels were extremely low and showed little or no correlation to clinical response. Hematologic findings, including complete blood count, hematocrit, platelet count, bleeding and clotting time and prothrombin levels, were normal.

TABLE 1. *Drug Tolerance in Relation to Clinical Improvement in 15 Patients.**

TYPE OF REACTION	NO. OF CASES†	PATIENTS CLINICALLY IMPROVED
Diarrhea	3	3
Rectal itching	3	3
Nausea and anorexia	3	3
Gaseous indigestion	2	2
Abdominal pain	1	1
Weakness and dizziness	1	1

*Twelve patients were completely asymptomatic.

†Reactions listed include those found only in 3 patients — 2 with pruritus ani only, and 1 only on high dosage exhibited all reactions.

DISCUSSION

These early observations suggest that Magnamycin may prove to be the drug of choice against enterococcal urinary infections. The percentage of clinical improvement with bacteriologic sterility is high, and the number of relapses low. Magnamycin therefore seems to fill a narrow but important void in the present armamentarium against genitourinary infections. The usefulness of in vitro sensitivity tests as a guide in therapy is once more demonstrated. In general, Magnamycin blood and urine levels were found to be of questionable value as indications of response to the drug. Many patients responded favorably despite insignificant or even negative values.

SUMMARY

Magnamycin appears to be a good antibiotic for gram-positive urinary tract infections particularly the enterococcal group. The drug is generally well tolerated, no serious reaction being encountered.

There appears to be good correlation between in vitro sensitivity and response to therapy.

BY THE LONDON POST

College of General Practitioners—Fifty Years of Medicine—Discovery of Penicillin—Postscript

JOHN LISTER, M.D.

LONDON, ENGLAND

THE most constructive suggestions for calling a halt to the lowering of status of general practice that has been evident in this country for the last few years are contained in the Report of the General Practice Steering Committee (1952) recently published in the *British Medical Journal*.[1] The Committee consisted of a group of general practitioners and a number of specialists under the chairmanship of Mr. H. U. Willink, a former minister of health. The Committee accepted the American Academy of General Practice's definition of a general practitioner as "a legally qualified doctor of medicine who does not limit his practice to a particular field of medicine or surgery" but added recognition of certain unique features in the role of the family doctor: "He must be prepared to assume some degree of responsibility in any and every illness, in people of all ages, over long periods of time; he must play his part in preventive medicine; and he must help in social difficulties. His deliberate aim should be to achieve breadth of vision rather than great depth in any particular sphere."

The Committee proposed that a general practitioners' organization be set up and that it be entitled a "college of general practitioners." They hoped that the College would give a lead to general practice and stressed the academic and educational rather than the political aspects of its function. They also hoped that the College would assist in the training of undergraduate medical students for general practice and suggested that, before long, experienced practitioners might be accepted as members of the staffs of teaching hospitals. They also suggested that the College could help to sponsor research by general practitioners in co-operation with the Medical Research Council and research departments of the universities. Many other activities are planned, and the hope is expressed that the foundation of this college will raise the prestige of the general practitioner and lead to an improvement in the quality of general practice.

Foundation members are invited to join the College from January 1, 1953, the temporary address, kindly offered by the Society of Apothecaries, being 14 Black Friars Lane, London E.C.4.

* * *

In the Harben Lectures delivered at the Royal Institute of Public Health and Hygiene in December, Lord Horder reviewed the progress of medicine over the last half century. Few doctors could be as well qualified to do so as he, for he obtained his

license to practice in 1896! He pointed out that although many epidemic diseases of previous centuries have disappeared, the automobile has almost replaced the microbe as a menace. Speaking of the Health Service, he wished that it had evolved more slowly, with extension of the family doctor's responsibilities to cover dependents of those covered by the older national-insurance scheme as a first step.

The diagnostic facilities and methods of treatment available in hospitals today have made the public dangerously dependent on them, and he called for a far better integration of the work of the family doctor, the specialist and the hospital. He believed that the National Health Service could create conditions favorable to such an integration but that at present perhaps the weakest feature of the Service was that it is not sufficiently fostering the evolution of a scheme that would enable doctors to give of their best without frustration and rigid control at the center.

* * *

Lord Webb-Johnson, after reading an article on penicillin by Sir Howard Florey,[2] wrote a letter of remarkable interest. He stated that the Royal College of Surgeons has four volumes in manuscript of Lister's laboratory diaries, which Lister called his "Commonplace Books." Here it is recorded that on November 21, 1871, Lister collected a specimen in a sterile flask and poured about half an ounce into each of six glasses. Some were covered, and others left exposed for varying times. Four days later he found a growth of Penicillium in one glass, and, examining a drop of the fluid microscopically, he recorded that: "It is rather curious that though the form of the bodies declared them to be bacteria I did not see any characteristic movements." Lister then embarked on an experiment "with the view of ascertaining whether the growth of fungi renders the liquid a less favorable nidus for bacteria." Although his experiment was inconclusive he observed that in a glass with only slight growth of Penicillium the bacteria "exhibited the most amazing energy" whereas those in a glass with profuse growth were "comparatively languid, multitudes were entirely motionless and there was not the same appearance of dense groups."

Lord Webb-Johnson relates in his letter how he showed these notes to Sir Alexander Fleming, who remarked that if fate had been kind to him Lister might have lived to see what he was always looking for — a nonpoisonous antiseptic.

* * *

Even in the National Health Service it is customary for a patient to bring to the hospital specialist a letter of introduction from his own doctor — usually with a brief history of his complaint.

The shortest version of such an introduction of which I have yet heard was about a patient who handed the specialist a visiting card that bore his doctor's name and address and carried on the reverse side the three words, "Over to you!"

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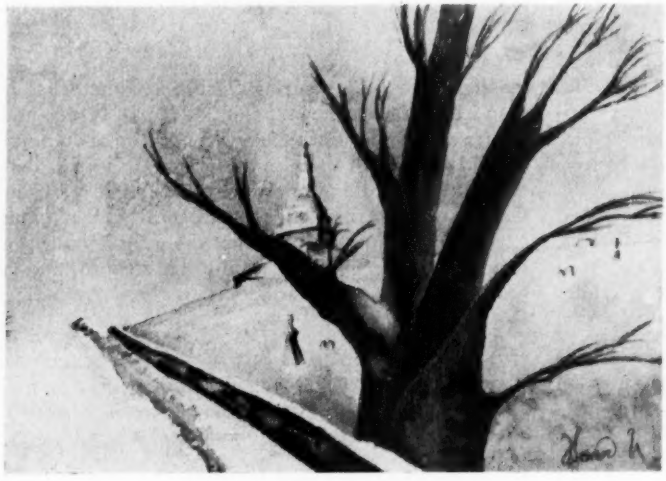

Massachusetts Physicians Art Society

12. *The Church Yard in Winter*

Exhibited at Massachusetts Medical Society, 1952

Water Color by
Howard Ulfelder, M.D.

Clinical Associate in Gynecology, Harvard Medical School; Assistant Surgeon, Massachusetts General Hospital; Junior Physician, Pondville Hospital

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39091

PRESENTATION OF CASE

A fifty-three-year-old housewife was admitted to the hospital because of abdominal pain.

For nine months before admission, the patient had had episodes of diffuse, periodic, crampy abdominal pain lasting two or three days. These were associated with diarrhea and occasionally awakened her at night. During the past summer she omitted fresh vegetables from her diet because she believed they caused her discomfort. Two months before admission the abdominal distress began to localize in the region of the umbilicus, and pains became more frequent. Diarrhea became worse although she had a normal stool when she first arose in the morning. When pain was absent she usually did not have diarrhea. At times, when she was awakened at night, pain and diarrhea often persisted until morning. On some days she was free of discomfort. There was no history of weight loss.

In the past the patient had usually had regular bowel movements, had not been constipated and had had diarrhea only occasionally. Ten years before entry she was examined for unknown symptoms, and at that time a diagnosis of "spastic colon" was made. Fifteen years before admission a hysterectomy had been performed.

Physical examination showed a well developed and well nourished woman in no acute distress. The heart and lungs were normal. In the abdomen the cecum was palpably enlarged and acutely tender but not abnormal in shape. On rectal examination there was acute tenderness about 7 cm. above the anus.

The temperature, pulse and respirations were normal. The blood pressure was 150 systolic, 80 diastolic.

The urine had a specific gravity of 1.010 and gave a + test for albumin; the sediment contained 25 red cells and occasional white cells per high-power field. Examination of the blood revealed a hemoglobin of 13.5 gm. and a white-cell count of 6300, with 71 per cent neutrophils, 19 per cent lymphocytes, 8 per cent monocytes and 2 per cent eosinophils. A roentgenogram of the chest was normal. A gastrointestinal series showed a normal esophagus, stomach, duodenum and upper small bowel. A plain film of the abdomen revealed normal bony structures. There was no enlargement of the liver or spleen, and both kidneys appeared normal. On barium-enema examination, barium flowed easily into the cecum. There were numerous diverticula in the descending and sigmoid colon. Within the cecum in the region of the terminal ileum, there was a spherical mass measuring 6 cm. in diameter (Fig. 1 and 2) that was constant on all films. It was not tender and could not be felt through the abdominal wall. It appeared to be in close relation to the ileocecal valve but did not produce obstruction. Barium flowed readily through the ileocecal valve. The examiner could not tell whether the mass lay outside or inside the cecum. Its outline was smooth, and it did not appear to be adherent to the surrounding tissue.

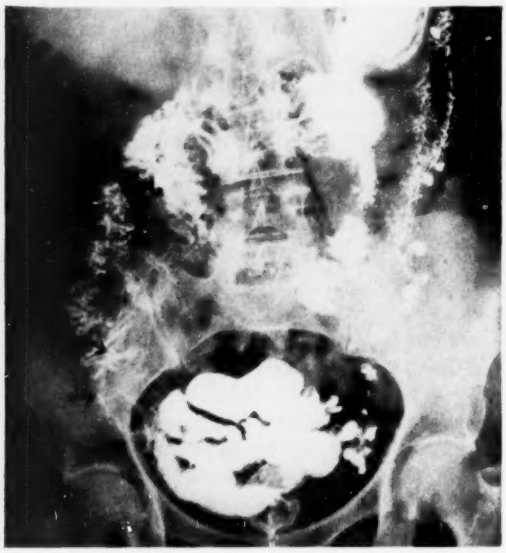

FIGURE 1. *Roentgenogram from Barium-Enema Examination. Arrows point to the margin of the ovoid shadow.*

On the third hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. ROBERT R. LINTON*: This case report presents the history and findings of a middle-aged woman with a surgical lesion of the gastrointestinal tract. It is of interest that the history was fairly

*Visiting surgeon, Massachusetts General Hospital.

recent in that the symptoms began nine months before she was seen and increased sufficiently to warrant admission to the hospital at the end of that time. Certainly, the history of bouts of diarrhea suggests some type of intermittent bowel obstruction. The diagnosis of a spastic colon was made ten years before admission, but I do not think this helps me at all in determining the diagnosis at this admission. She had a hysterectomy fifteen years before admission, but nothing is said about whether the appendix was removed at that time. Is there anything in the record to that effect?

FIGURE 2. *Spot Film of the Region of the Ileocecal Valve. Arrows point to the margin of the ovoid shadow.*

DR. BENJAMIN CASTLEMAN: I do not believe that the appendix was removed. I notice in the record that the hysterectomy was done for carcinoma of the endometrium and was followed by x-ray treatment in this hospital.

DR. LINTON: Are you letting the cat out of the bag here?

DR. CASTLEMAN: No; I had not known of this before.

DR. LINTON: Whether or not the appendix was removed is probably of no significance since no statement is made in the record, but appendicitis is one of the diagnoses that must be considered. There apparently was a little difference of opinion regarding the local abdominal signs since the surgeon or whoever wrote up the physical examination found definite signs of an inflammation in the right lower quadrant as evidenced by tenderness, even acute tenderness, whereas the radiologist, when the patient had barium-enema studies, reported that the mass in the right lower quadrant was not tender. The urine examination was reported as showing 25 red blood cells per high-power field, but I find no other report about this finding. Was an intravenous pyelogram taken?

DR. STANLEY M. WYMAN: No.

DR. LINTON: There is also a confusing statement in the barium-enema report; in one place the record states, "Within the cecum in the region of the terminal ileum, there was a spherical mass measuring 6 cm. in diameter," and, later it is stated, "The examiner could not tell whether the mass lay outside or inside the cecum." I think we had better see those x-ray films to decide.

DR. WYMAN: These films were from an examination done at another hospital; the patient had no x-ray examination in this hospital at this time. There is a sharply defined ovoid shadow, the margin of which is extremely well seen, lying in the region of the cecum, perhaps in the region of the ileocecal valve as the original examiner thought (Fig. 1). These spot films show the mass adequately (Fig. 2). The mass, I am quite certain, lies inside the cecum to produce this sharply defined outline.

DR. LINTON: Thank you, Dr. Wyman. There is another very important laboratory examination that is missing — the stool examination for blood. Was any performed?

DR. GORDON A. DONALDSON: Examinations were done, and were negative.

DR. LINTON: This simple test is one of the important methods of differentiating an ulcerating lesion from a nonulcerating lesion within the bowel.

It seems to me that the possibilities of diagnosis are limited because the lesion was obviously in the region of the ileocecal valve. As I first read the history, and before I saw the x-ray report, I wondered whether the patient had regional enteritis, but the history is short for the disease and the patient older than usual in my experience for this diagnosis. The white-cell count was within normal limits, and it is also of some significance that the hemoglobin was normal, indicating the probable absence of an inflammatory disease and of an ulcerating malignant lesion of the bowel. The x-ray findings substantiate my opinion that this was not regional enteritis because the small bowel was normal, and the positive x-ray findings were limited to the terminal portion of the ileum, or even the ileocecal valve. In view of the negative guaiac test on the stool and the absence of anemia, I think I shall rule out carcinoma of the cecum although I was tempted to make such a diagnosis.

The appendix had not been removed at the time of the hysterectomy. It should be remembered that the appendix is the source of several types of disease. One is acute appendicitis, which I do not think this patient had because the history was too long and the physical findings were not consistent with it. Another possibility is a carcinoid of the appendix,

which I think is a diagnosis that one has more or less to guess at, since I do not know any clear-cut way to make that diagnosis before operation. Even when one has the appendix in his hand, it is not too easy to make this diagnosis, but I should think it is a possibility. Carcinoma of the appendix can also occur, although it is extremely rare; I should think one would have to rule it out on the rareness of the condition.

The mass may have been a leiomyosarcoma or a tumor of that nature, but again there is usually bleeding with these lesions. A lipoma, another possibility, can occur in almost any location in the body and not infrequently occurs in the large bowel, usually giving signs of intussusception somewhere further along in the course of the colon. I had considered some of the retroperitoneal tumors but I think they are unlikely in view of the roentgenographic findings.

It seems to me in conclusion that the best I can say is that we are dealing with a surgical condition about whose pathological nature I have great difficulty in coming to any definite, clear-cut conclusion. I believe it probably was a slowly growing lesion in the region of the ileocecal valve. The fact that there was no blood in the stool and that there was no anemia makes me think it was not an ulcerating lesion. I believe it was a benign lesion and will make a diagnosis of a lipoma in the region of the ileocecal valve.

Dr. Walter Bauer: Is not carcinoid of the appendix more likely than lipoma?

Dr. Linton: I did not think carcinoid of the appendix would produce such a pressure lesion as this in the ileocecal valve.

Dr. Castleman: Carcinoids of the appendix are usually fairly small and rarely occur in the base, where this would have to be, and rarely enlarge sufficiently to produce such a large filling defect. The only way such a filling defect could arise would be from a mucocele of the appendix distal to the carcinoid, which might then bend back along the cecum, but then the lesion would be extrinsic rather than intrinsic.

Dr. Wyman: I agree with Dr. Castleman. This seems to be intraluminal, an actual mass in the cecum at the level of the ileocecal valve as far as the examiner can tell.

Dr. Bauer: That would never invert?

Dr. Castleman: No. Carcinoid of the bowel itself would be something else again; as a rule the size of the original carcinoid in the bowel is small. What usually causes the pressure defect is metastases of the carcinoid to the regional lymph nodes in the mesentery, which are usually not so close to the ileocecal valve; they are usually in the terminal ileum above the ileocecal valve.

A Physician: How about a fecalith or a gallstone in the cecum?

Dr. Wyman: I suppose it is possible. I do not believe I have ever seen one in this location.

Dr. Linton: I think there would be considerable dilatation of the terminal ileum and signs of partial obstruction with a foreign body such as either of those lodged in the terminal ileum at the ileocecal valve.

Dr. Donaldson: Do you think, Dr. Linton, that the patient had obstruction?

Dr. Linton: I do not believe that the patient was completely obstructed when she was operated on; there may have been a slight degree of obstruction but we have no evidence of it by x-ray examination.

Dr. Donaldson: I should like to make a case in defense of the precipitous attack upon this patient. She was transferred from another hospital, where she had been for three days, so that the total work-up was five days and the guaiac test on the stool was negative. The relation of the pain and watery diarrhea was quite dramatic; the episodes occurred in attacks, after which she was perfectly well for a matter of weeks. However, the attacks were becoming more frequent and more constant, and these x-ray films were taken.

A Physician: Do you think tuberculosis in the cecum may cause a mass?

Dr. Castleman: There is a hyperplastic form of tuberculosis, but I do not think the mass would be as smooth as this; ordinarily there is some ulceration and some hemorrhage into the gastrointestinal tract.

Dr. Wyman: I think that is entirely true.

Clinical Diagnosis

Lipoma of ileocecal valve.

Dr. Robert R. Linton's Diagnosis

Lipoma in region of ileocecal valve.

Anatomical Diagnosis

Redundant lipomatous ileocecal valve.

Pathological Discussion

Dr. Castleman: This is the specimen that was removed at operation by Dr. Donaldson, showing the terminal ileum, ileocecal valve and cecum (Fig. 3). The ileocecal valve was large, measuring 5 cm. in circumference, and was quite movable and probably led to intermittent intussusception. The enlargement was produced by a tremendous deposition of submucosal fat tissue. We have seen a number of these cases and are uncertain whether these are true lipomas or whether they are merely fatty ileocecal valves. Microscopical section of the valve showed a large amount of fat in the submucosa. Normally there is some fat in this region, and this may just be a variation of the normal. We prefer to call these redundant lipomatous ileocecal valves, but it is important to realize that they may produce attacks of intussusception.

DR. WYMAN: I should like to congratulate Dr. Linton. I think the picture is suggestive if not diagnostic in the x-ray films. The extremely sharply defined mass, which lies in the cecum in the region of the valve, presumably in the valve, makes a fatty ileocecal valve about the only diagnosis to consider. I think if one can identify the relation of this mass to the ileocecal valve and then can see a good sharp clear outline, he can make a diagnosis with assurance. The only point lacking in the diagnosis of lipoma is the radiolucency usually noted when fat is in a part of the body sufficiently available for free roentgenography. In this site the small accumulation of fat buried in the body makes this observation in all probability difficult or impossible unless the mass is large and the patient small. The degree of contrast is not sufficiently great. The Radiology Department has been interested in this condition and has found quite a few cases. Dr. Emery Lewis and Dr. H. Peter Mueller found about 10 in one year.

FIGURE 3. *Terminal Ileum, Ileocecal Valve and Cecum.*

DR. CASTLEMAN: They found them by x-ray examination; how many patients were operated on?

DR. WYMAN: I do not know how many were operated on and how many were observed by x-ray examination alone.

CASE 39092

PRESENTATION OF CASE

A sixty-three-year-old baker was referred to this hospital because of postoperative coma.

One month before admission the patient consulted his physician because of postprandial epigastric distress and periodic vomiting of bile-stained material induced particularly by fried foods. On physical examination an enlarged liver extending three fingerbreadths below the costal margin was found. X-ray examinations of the chest and gastrointestinal tract were negative, but a cholecystogram showed a nonfunctioning gall bladder with stones. Five days before entry he was admitted to another hospital, where a cholecystectomy was performed. During laparotomy, a "hobnail liver" was encountered, and while the gall bladder was being freed from numerous adhesions it was ruptured, with spillage of its contents into the peritoneal cavity. There was profuse bleeding from the gallbladder bed that was checked only by packing with Gelfoam since sutures in the liver would not hold. A large catheter left in the wound continued to drain serosanguineous material. Postoperatively the blood pressure dropped to low levels. The patient received 500 cc. of blood during surgery and a like amount later, when the temperature rose to 103°F. On the first postoperative day, he was alert, afebrile and restless and had nausea and vomiting. He was hypotensive; his pulse was rapid. He was anuric for forty-eight hours postoperatively but resumed a good output thereafter. The immediate postoperative regimen included 2000 cc. of fluid a day, streptomycin, penicillin and digitalis. He was given 95 mg. of morphine on the first postoperative day, 15 mg. of morphine sulfate, 60 mg. of Pantopon, 60 cc. of phenobarbital and 2 cc. of morphine-scopolamine preparation on the second postoperative day, and single doses of 300 mg. of Amytal on the third and fourth days. On the fourth postoperative day he was alert, but that night he began to show signs of confusion and depressed consciousness, lapsing into coma at midnight. He responded only to painful stimuli and was incontinent of urine. Icterus was observed for the first time. After operation he had hiccups and vomited bile-stained fluid daily.

He had been a heavy drinker for many years but had allegedly stopped drinking eighteen months before admission. He had undergone a left nephrolithotomy four years before entry.

Physical examination revealed an acutely ill, dyspneic man who hiccuped occasionally, groaned constantly, seemed unaware of his surroundings and responded only to extreme stimuli. There was scleral icterus and one vascular spider on the right shoulder. The right pupil measured 5 mm., and the left 4 mm. in diameter; both reacted to light but remained fixed in the primary position. The optic

disks were flat; the arterioles showed spasm and arteriovenous nicking. There were no exudates or hemorrhages. The neck was resistant but not rigid. The heart and lungs were normal. The abdomen was soft and apparently nontender. The liver edge was hard, irregular and palpable at the level of the umbilicus. Serosanguineous fluid drained from the right-upper-quadrant wound. The extremities were normal.

The temperature was 102°F., the pulse 100, and the respirations 30. The blood pressure was 125 systolic, 70 diastolic.

A urine specimen had a specific gravity of 1.010 and gave a + test for bile, a green sugar test (25 per cent dextrose in water was being infused intravenously at the time of the test), and a negative test for albumin; the sediment contained 2 to 5 red cells and 4 to 8 white cells per high-power field. Examination of the blood showed a hemoglobin of 11 gm. per 100 cc. and a white-cell count of 19,400, with 81 per cent neutrophils and 19 per cent lymphocytes. The nonprotein nitrogen was 58 mg., the serum bilirubin 0.7 mg. direct and 1.2 mg. total, the alkaline phosphatase 10.3 units, the total protein 5.4 gm., the albumin 2.2 gm., and the globulin 3.2 gm. per 100 cc., with an albumin-globulin ratio of 0.7; the sodium was 133.3 milliequiv., the potassium 3.0 milliequiv., the chloride 90 milliequiv., and the carbon dioxide 35.9 milliequiv. per liter. The bromsulfalein retention was 51 per cent, and the cephalin flocculation was ++. The stool guaiac test was negative on admission and was ++ later. A spinal-fluid examination showed clear fluid under an initial pressure equivalent to 140 mm. and a final pressure equivalent to 80 mm. of water. The fluid contained 866 red cells per cubic millimeter thought to be due to a traumatic tap; the total protein was 34 mg., and the sugar 110 mg. per 100 cc.

The patient was given tube feedings and intravenous infusions of 25 per cent dextrose and saline solution as well as aureomycin, Gantrisin, penicillin, chloramphenicol and Synkavite (water-soluble vitamin K compound), and within forty-eight hours he was normotensive and much improved clinically. He was able to take food, and intravenous infusions were stopped. The drainage from the cholecystectomy wound remained clear, straw-colored fluid. On the seventh hospital day the blood pressure fell to 80 systolic, 50 diastolic; the pulse was 88 per minute, and the temperature 100°F. The white-cell count was 17,500. The carbon dioxide was 31.3 milliequiv., the chloride 104 milliequiv., the sodium 133.6 milliequiv., and the potassium 4.0 milliequiv. per liter, and the pH 7.55. The cephalin flocculation was +++ in twenty-four and ++++ in forty-eight hours, and the serum bilirubin 1.1 mg. direct and 1.5 mg. total per 100 cc. He was again treated with intravenous infusions of 25 per cent dextrose and saline solution, after which his condition improved, the blood pressure stabilized at 100 systolic, 70 diastolic, and he was able to sit up in a chair. Culture of the wound drainage showed a few colonies of *Staphylococcus albus* and nonhemolytic streptococci. Later, the drainage became serosanguineous, and on the thirteenth hospital day the wound dehisced, requiring resuturing. Shortly after operation he became hypotensive but again responded to intravenous infusions of fluids. On the following day the nonprotein nitrogen was 90 mg. per 100 cc., and the serum sodium was 124.6 milliequiv., the potassium 6.7 milliequiv., and the chloride 94 milliequiv. per liter. The patient became distended, chiefly in the left upper quadrant. Rectal examination showed soft feces in the ampulla. Roentgenograms demonstrated marked distention of the right and transverse portions of colon in the region of the splenic flexure. There were some loops of distended small bowel in the lower abdomen. There was no evidence of fluid in the abdomen, and the properitoneal fat lines were intact. On barium-enema examination the barium passed readily from the rectum to the splenic flexure but did not pass beyond this point. No filling defect was seen.

Vomiting without nausea developed, and on the twenty-second hospital day, under local anesthesia, a cecostomy was performed, but no mechanical obstruction was found. After this, the blood pressure fell as low as 50 systolic, 30 diastolic, but stabilized at 70 systolic, 40 diastolic. The urine output was 540 cc., and the temperature 103°F. The patient was pale, oriented and alert. An electrocardiogram showed nonspecific ST-segment and T-wave changes compatible with but not diagnostic of coronary-artery disease.

Cephalic-vein cutdowns were performed to facilitate parenteral feeding, after which the blood electrolytes returned to normal. The patient's state of consciousness improved, he was able to take oral feedings, and he passed one stool by rectum. On the thirty-second hospital day the temperature rose to 102°F., there was ++++ pedal edema, and he again became distended. The urine sodium output was 0.4 gm. compared to an 8-gm. oral intake. The specific gravity of the urine remained at 1.008. Two days later, the serum sodium was 124.6 milliequiv. per liter, and the blood pressure 95 systolic, 60 diastolic. Anasarca persisted, and because the patient was thought to have a "low-sodium syndrome," he received 300 cc. of 6 per cent sodium chloride. The blood pressure subsequently rose to 120 systolic, 80 diastolic, the pulse was 120 and the state of consciousness improved. The urine output was 880 cc. in twenty-four hours with a specific gravity of 1.018. However, his sensorium again clouded. A gastric tube was passed, and 20 to 30 cc. of dark-brown material was aspirated. On the following night (the thirty-seventh hospital day) he had a shaking chill. The left-cephalic-vein cutdown site was swollen. Blood cultures, previously negative, grew *Staph. aureus*. A left-axil-

lary-vein ligation was performed. Blood chemical determinations at this time showed a sodium of 158.5 milliequiv., a chloride of 116 milliequiv., a potassium of 3.5 milliequiv., and a carbon dioxide of 27.5 milliequiv. per liter, and a nonprotein nitrogen of 35 mg. and a total protein of 6.1 gm. per 100 cc. with an albumin-globulin ratio of 1.0. The urine sodium was 41 milliequiv., and the potassium 57 milliequiv. per liter on an 850-cc. twenty-four-hour specimen.

The patient continued to be disoriented and vomited coffee-grounds material, after which he was cyanotic. Moist rales were heard in both lungs. Bronchoscopic aspiration improved him temporarily. He was oliguric and died on the thirty-ninth hospital day.

Differential Diagnosis

Dr. John Homans, Jr*: This story begins with a cholecystectomy on a sixty-three-year-old man who had a history of alcoholism and in whom a large hobnail liver was found at operation. There is no indication in the record that the patient was chronically ill before the attacks of abdominal pain and vomiting that brought him to surgery. The operation was a difficult one, with rupture of the gall bladder and profuse bleeding from the gall-bladder bed, which might well indicate a lowered prothrombin concentration. I might state here that my opinion about the subsequent history is that it can be explained on the basis of the complications resulting from operating on a man with poor liver function. Postoperatively he went into shock and anuria, relieved by a transfusion and 2000 cc. of other fluids. It is stated that he was given large amounts of narcotics and moderately large doses of barbiturates. Since all these except for the phenobarbital are detoxified mostly in the liver it is surprising that he did not show more over-reaction to them. The semicoma in which he was admitted began only on the fourth day, on which he received only 300 mg. of Amytal and I would imagine that the state of consciousness was dependent more on liver failure than on drugs.

Physical examination at this hospital apparently gave no sign of peritonitis. Except for one determination toward the end of the course, the urinary specific gravity seems to have been fixed at about 1.010, but the negative test for albumin should rule out any severe lower-nephron nephrosis, as a result of the previous episode of shock or transfusion reaction, and it should rule out any pre-existing kidney disease. The elevated phosphatase and reversed albumin-globulin ratio with low albumin are consistent with severe liver disease. The low blood sodium and chloride concentration seems to have been combated periodically throughout the rest of the course first with physiologic saline solution and finally with hypertonic saline solution. The potassium, first low, was later high and finally low; I cannot make anything of this. I think that the low sodium and chloride, with the gradually developing edema, represent a failure of the kidney to regulate the excretion of water and salt to the effect that the patient was losing more salt than water in the urine and was losing both into his body fluids. The only explanation that I can see for this failure of tubular function is lack of adequate circulation to the kidney, particularly during the episodes of low blood pressure, added to the deficient albumin. I do not believe that adrenal failure need be implicated. The low potassium on admission, the normal blood pressure and the normal spinal-fluid sugar, provided that he was not receiving a 25 per cent glucose solution intravenously at the time, are specifically against this. The bromsulfalein retention of 51 per cent with minimal jaundice and the increasingly positive cephalin-flocculation test represent a severe depression of liver function. The resistant neck and the lumbar-puncture findings, I believe, are not important.

The patient improved on a regimen of intravenous infusions of glucose and salt, a full battery of antibiotics and vitamin K. On the seventh hospital day there was another episode of low blood pressure. The sodium was again somewhat low, and both the carbon dioxide and chloride were on the high side, with a somewhat alkaline pH. I suspect the chloride of being in error. He was treated with glucose and physiologic saline solution, again with improvement. On the thirteenth day the wound dehisced, requiring a second operation on this very sick man and hastening his now inevitable decline. Distended loops of large and small bowel developed, owing, I think, to a paralytic ileus, because during colostomy no mechanical cause for obstruction was found. After this third operation the blood pressure again fell, and the urine output became insufficient, with a rise in the nonprotein nitrogen to 90 mg. per 100 cc. He again improved on parenteral feeding with lowering of the nonprotein nitrogen but now developed edema and was retaining most of the sodium injected. When the blood concentration of sodium became really low he was given 18 gm. of salt, evidently in one injection, which restored his state of consciousness and blood pressure but overshot the mark, producing a sodium of 158 milliequiv. per liter. The urine sodium concentration of 41 milliequiv. per liter or an excretion of about 35 milliequiv. per day was less than one would expect at this high level of blood sodium concentration. Terminally, a thrombophlebitis of the cephalic vein developed, with blood cultures positive for *Staph. aureus* presumably coming from this source. He began to bleed into his stomach, vomited and probably died of aspiration of some of the stomach contents.

I do not believe that any disease but cirrhosis of the liver associated with alcoholism is necessary

*Assistant in medicine, Massachusetts General Hospital.

to explain this patient's course. Once he was operated on I believe that he died of liver failure with the complications of wound dehiscence, paralytic ileus and cephalic thrombophlebitis, which could be expected in this condition. The chemical and renal findings were certainly not sufficient to cause death but represented a secondarily deficient renal function subsequent to hepatic failure possibly caused by an inadequate blood supply to the tubules. There was no convincing evidence of general or localized infection except terminally to account for the high white-cell count and occasional episodes of fever, unless there had been an acute necrotic process going on in the remaining liver tissue.

There was no evidence for a malignant process either in the liver or elsewhere that I can see. The bleeding at the original operation and the terminal gastric bleeding should be related to the liver disease, either diffuse bleeding associated with a lowered prothrombin concentration, or bleeding from varices.

Dr. Arthur Haut: Whereas at first it seemed that this patient's course was explainable solely as the sum of the postoperative complications to which a person with advanced hepatic cirrhosis would be subject, our views changed as we observed the fluctuations in his condition. We were impressed by the hyponatremia and hypotension and the general deterioration of his condition, changing for the better after the administration of large amounts of salt parenterally (12 to 15 gm. daily), and then recurring when the supplements were stopped. We devoted considerable attention to the management of the electrolytes because they seemed to be so closely related to his clinical well-being: a much closer relation than we ordinarily see in cirrhosis alone. We postulated, as Dr. Homans does, that the kidneys were unable to conserve salt, and attributed this to damage to renal tubules incident to the forty-eight-hour episode of hypotension and anuria following the cholecystectomy. Opinion was divided about the possibility that adrenal failure was responsible for the salt losses and hypotension, but the consensus was that such a possibility was inconsistent with the patient's demonstrated ability to tolerate and survive the operations and their many complications; however, cortisone was ordered at one point.

Aside from the serum electrolyte situation — which we could never adequately stabilize — the succession of complications (narcotic overdosage, wound dehiscence, paralytic ileus and gastrointestinal bleeding) were each adequately handled, in turn, until septic thrombophlebitis dealt the final blow to this debilitated man.

Clinical Diagnoses

Hepatic failure, due to Laënnec's cirrhosis.
Septic thrombophlebitis, left brachial vein.
Staph. aureus septicemia.
?Large-bowel obstruction.
Lower-nephron nephrosis.

Dr. John Homans, Jr.'s, Diagnoses

Cirrhosis of liver, alcoholic.
Paralytic ileus.
Cephalic thrombophlebitis.

Anatomical Diagnoses

Hepatoma, with invasion of portal, splenic and adrenal veins.
Massive metastases to both adrenal glands, with adrenal failure.
Portal cirrhosis, alcoholic type.
Cephalic thrombophlebitis (caused by *Staph. aureus*).
Acute bacterial endocarditis, aortic valve (due to *Staph. aureus*).
Metastatic abscesses to heart and adrenal glands (due to *Staph. aureus*).
Ascites and hydrothorax.
Operations: Cholecystectomy, recent.
Cephalic-vein cutdowns, recent.
Ligation, right brachial vein, recent.
Cecostomy, recent.

Pathological Discussion

Dr. Winfield S. Morgan: At autopsy the peritoneal cavity contained approximately 1000 cc. of clear, amber fluid, and each pleural cavity about 750 cc. of similar fluid. Aside from slight hydronephrosis on the right and mild nephrosclerosis the kidneys were not remarkable. The lungs showed severe congestion and edema. The heart was not enlarged, but the aortic valve was partially calcified and there was interadherence of the cusps compatible with an old rheumatic endocarditis. On the edge of the valve there were several soft, friable, yellowish-brown vegetations measuring 2 to 3 mm. in greatest dimension. Microscopically, these consisted of fibrin and masses of bacteria, and represented an acute bacterial endocarditis that undoubtedly originated in the septic thrombophlebitis of the arm. There were metastatic abscesses in the myocardium and left adrenal gland.

The findings of chief interest were in the liver and came as a surprise to us since in reviewing the clinical history we shared Dr. Homans' opinion

that this probably represented a case of complications of gall-bladder surgery in the presence of a failing alcoholic liver. The liver weighed 1900 gm.

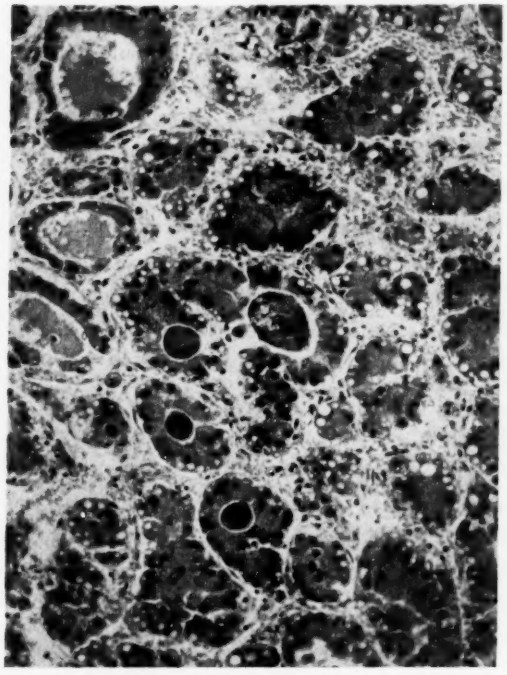

FIGURE 1.

and was nodular, showing the gross picture of alcoholic cirrhosis. However, this was modified to some extent by the presence of diffuse nodules of yellow-red, often necrotic tumor, which replaced much of the liver substance. The radicles of the portal vein in the liver were filled with tumor, and tumor had extended distally, occluding the portal vein for a distance of 2.5 cm. There was further extension into the splenic vein. The adrenal veins were filled with tumor, and there was a tumor thrombus 2 cm. long in the vena cava at that level. Both adrenal glands were markedly enlarged, the right weighing 95 gm. and the left 46 gm. On section they were completely replaced by tumor, which undoubtedly accounted for the syndrome of hyponatremia, hypotension and so forth.

Our gross impression was that the tumor was a hepatoma, and on microscopical examination, this was confirmed. It was composed of large cells showing a marked tendency to form glands, the lumens of which often contained bile (Fig. 1). One interesting observation was the presence in the hematoxylin-eosin sections of vacuolated spaces in almost every tumor cell, which proved to be filled with fat, and resembled very closely the fatty change observed in the cells in the cirrhotic, non-neoplastic portions of the liver.

Several years ago Dr. Tracy B. Mallory was presented with a slide of a metastatic tumor in the spine and chiefly on the basis of the vacuolization believed that it was a metastatic hepatoma — which it turned out to be. Although fat vacuolization is not a rare finding in tumors, particularly in certain stages of degeneration, the degree that the tumor in the case under discussion showed suggests that in some cases of hepatoma the tumor cells react to influences producing fatty change in the same way that the liver cells do.

Evaluation of Clinicopathological Exercises. To evaluate the place of the clinicopathological conference in medical education, Dr. Castleman would like to obtain a list of the groups that use the Case Records of the Massachusetts General Hospital as a teaching exercise in their society or hospital meetings, dinner clubs, student conferences and so forth. If it becomes practical, would your group be interested in obtaining pertinent lantern slides of roentgenograms, specimens and so forth with each case? Replies indicating the method used in the group should be made directly to Dr. Castleman, Massachusetts General Hospital, Boston 14. Comments and suggestions will be welcome.

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COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6 2094.

FIRESIDE CHAT

SINCE the 1890's, when the subscription price of the *Boston Medical and Surgical Journal* was $5.00 per annum, $3.00 has by slow stages been added to the full rate. Students, interns and fellows of the Massachusetts Medical Society still receive this weekly offering at $5.00 per year, post paid.

Obviously, consistent efforts must have been made to keep the subscription rate of a weekly scientific publication as low as it is in view of the well known increases in the costs of production. It need be no secret that the fulfillment of each subscription cost the *Journal* $5.97 in 1949, $6.13 in 1950, $6.54 in 1951 and $7.32 in 1952.

Any undertaking of any great magnitude is subject to criticisms, complaints and suggestions, all of which, in the case of the *Journal*, receive serious consideration. Those regarding slow delivery in particular have been mounting, and improvement in this department can almost be assured, at least so far as delivery to the post office is concerned. From there on the United States Government takes over and has assured the nation, in respect to its delivery service, that "not snow, nor rain, nor heat, nor gloom of night stays these couriers from the swift completion of their appointed rounds."

Flat mailing of the *Journal*, as is the custom now with so many periodicals, including the *Journal of the American Medical Association*, was started in January. This was done to save the extra cost of wrapping as well as the time consumed by the manipulation, and to meet the complaints of those who objected to having their *Journal* sharply creased in the middle. There are now those who complain that journals arrive in a mutilated condition, as if the swift couriers of the Postoffice Department had committed mayhem on them. The managing editors, eager still to please, although trying also to keep subscription rates at their present level for as long as possible, will, if necessary, put a heavier cover on the *Journal* to act, possibly, as a sort of bullet-proof vest.

Everyone, of course, cannot be pleased, and efforts in this direction recurrently remind one of the fable of the father, his son and their donkey going to market and trying to overcome the prejudices of each passerby. The man rode and his son walked; the son rode and his father walked; they both rode, and they finally reached their destination carrying the donkey between them, slung over a pole.

Some of the complaints of subscribers concerning the service are about conditions that can and will be remedied; others result from the honest efforts made by the management to maintain the present unusually low subscription rates. Some of those who complain most feelingly are receiving the *Journal* at more than $2.00 a year below cost, at a loss that is barely met by a reasonable profit on advertising.

STUDENT MEDICINE

DURING the past few years a new focus of interest in medicine has been developing at a rapid rate — namely, the health of the college student. In most colleges until recently (and in many colleges now) the student who became ill was dependent upon his own immediate financial resources for treatment. If these were inadequate, the generosity of local physicians and faculty members was all that was between him and acute neglect. Gradually, the idea has been accepted that the college community should be responsible for its own medical care, giving rise to college infirmaries, medical staffs and prepayment or insurance plans for such medical care.

From this has quite naturally grown the concept that maintenance of health is everyone's business and that this is a far greater problem than the treatment of disease, important as that is. The college is the ideal place to set the standards of health maintenance and to help students learn how to use most effectively the many principles of hygiene that contribute to their physical, emotional and social well-being.

It seems particularly fitting, therefore, that there should be some recognized medium for the collection and dissemination of information of particular importance to college physicians. This function has been undertaken by the Department of Clinical and Preventive Medicine of Cornell University, which has recently published the first issue of *Student Medicine*, two publications yearly being planned. Judging from the quality of the first slender pamphlet, its success should be warmly encouraged. The *Journal* welcomes it with high hopes for its future.

INTERNATIONAL THINKING DAY

IN line with the prevailing custom of dedicating certain areas of time to specifically designated purposes, Washington's Birthday, February 22, has been named International Thinking Day. The source of this inspirational treatment was not revealed in the Red Feather newsletter that broke the story, but it is heart warming to realize the steady progress that the intellectual processes are making.

One need not contemplate those 364 other days when the people of many nations work in the fields or sit before the television or simply sit; it is enough to know that one day at least, in those free countries outside the iron curtain, is given over to the richly cultural experience of cerebration. It is also cheering to know that the birthday of this country's father has been selected for this thought-provoking activity, in view of G. W.'s well known thinking on internationalism and entangling alliances.

A new book, heralding a new theory, has originated at Rochester, N. Y., having the following title — "Exposition of Motorpathy: a new system of curing disease, by statuminating, vitalizing motion."

Boston M. & S. J., *March 2, 1853*

MASSACHUSETTS MEDICAL SOCIETY

SPECIAL AUTOMOBILE EMBLEM

A special emblem has been designed for members of the Massachusetts Medical Society to fill the space on the front of the physician's automobile, formerly occupied by the front license plate. Each plate will bear an identifying number, which will be kept on record at the headquarters of the Society.

This special plate may be purchased by fellows of the Society at a cost of $2.50 without frame, or $5 with frame, on direct application to the Wildon Products Company, 20 Vernon Street, Somerville 43, Massachusetts.

ROBERT W. BUCK, *Secretary* pro tempore

INFORMATION REGARDING DUES

There is still some confusion and a lack of complete understanding on the part of Fellows concerning dues payable annually to the Massachusetts Medical Society as distinguished from dues payable annually (since 1950) to the American Medical Association.

Before 1950, membership in the American Medical Association was automatic for all Fellows in good standing of the Massachusetts Medical Society. This is no longer the case.

A summary follows of our own regulations concerning dues, and those of the American Medical Association:

MASSACHUSETTS MEDICAL SOCIETY DUES

Resident fellows of the Massachusetts Medical Society received in January a bill for $35.00 fellowship dues. These dues must be paid by all members with the following exceptions:

(1) Fellows who are 65 years of age or older who have applied to the Treasurer and been specifically exempted from assessment.

(2) Fellows who are not in practice and whose low income would make it a hardship, if on request of the administrative head of the institution by which they are employed, the Committee on Membership has reduced the amount of their dues. No provision exists for the *remission* of dues in such instances.

(3) Fellows in active service in the United States Army, Navy or Public Health Service (except those going into service during the first year of fellowship).

AMERICAN MEDICAL ASSOCIATION DUES

Resident fellows of the Massachusetts Medical Society are on payment of an additional $25.00, entitled to membership in the American Medical Association. Therefore they received in January a bill for dues from the American Medical Association in the amount of $25.00. A check or money order for this amount should be sent, in accordance with the By-laws of the American Medical Association, "to the constituent association for transmittal to the Secretary of the American Medical Association." The check or money order should be made payable to the American Medical Association and mailed with the billhead to 22 Fenway, Boston.

If a member of the Massachusetts Medical Society has been excused from the payment of his full dues in our Society, the Board of Trustees of the American Medical Association may excuse him from payment of American Medical Association dues under the following circumstances only:

(1) If the payment of dues would constitute a financial hardship. This fact must be certified to by the secretary of the member's component society.

(2) If he is retired from active practice.

(3) If he is an intern or resident during the first five years following graduation except that the time spent in military service may be excluded in calculating the five year limit.

(4) If he is in the armed forces temporarily. A. M. A. dues will be remitted January 1 or July 1 following the date of the member's entrance into military service, regardless of local dues exemption.

(5) If he has reached his 70th birthday before January 1 and has requested remission of his A. M. A. dues. This remission may be granted regardless of local dues exemption.

Members of the Massachusetts Medical Society who have paid their dues of $35.00 in our Society do not lose fellowship in the Massachusetts Medical Society if they do not pay their $25.00 American Medical Association dues. They do, however, deprive the Massachusetts Medical Society of their representation in the House of Delegates of the A. M. A., since the number of delegates to which the Massachusetts Medical Society is entitled is based upon the number of its members who have paid their $25.00 dues to the American Medical Association, providing they have not been excused from such dues under the circumstances listed above.

NON-RESIDENT FELLOWS OF THE MASSACHUSETTS MEDICAL SOCIETY

This category includes all fellows who do not have a legal residence in Massachusetts. Their annual dues are $7.00. They are not thereby entitled to membership in the American Medical Association nor are they counted in our representation to the House of Delegates of that body.

DEATHS

EMMONS — Henry M. Emmons, M.D., of Boston, died on January 19. He was in his seventy-seventh year.

Dr. Emmons received his degree from Boston University School of Medicine in 1902. He was professor emeritus of surgical ophthalmology at Boston University School of Medicine and Massachusetts Memorial Hospitals and was a member of the New England Ophthalmological Society and a fellow of the American Medical Association.

He is survived by his widow, a son, a daughter and five grandchildren.

KAHN — Walter S. Kahn, M.D., of Lowell, died on January 5. He was in his fifty-seventh year.

Dr. Kahn received his degree from the Medical Faculty of the University of Bonn in 1921. He was a founding member of the World Medical Association.

He is survived by his widow.

KURTH — Gustave E. Kurth, M.D., of Lawrence, died on December 26, 1952. He was in his eighty-third year.

Dr. Kurth received his degree from Harvard Medical School in 1901. He was a former president of the Essex North District Medical Society and formerly senior surgeon at Lawrence General Hospital, and was a councilor of the Massachusetts Medical Society from 1914 to 1927. He was a fellow of the American College of Surgeons and the American Medical Association.

He is survived by a son, two brothers, two grandchildren and one great-grandchild.

MARIEN — Joseph E. Marien, M.D., of Fitchburg, died on December 26, 1952. He was in his forty-ninth year.

Dr. Marien received his degree from Boston University School of Medicine in 1930. He was a member of the staff of Burbank Hospital and was medical officer of Fitchburg Wing, Civil Air Patrol.

He is survived by his widow, three sisters and three brothers.

MAZZOLINI — Andres R. Mazzolini, M.D., of Holyoke, died on January 12. He was in his forty-eighth year.

Dr. Mazzolini received his degree from Middlesex University School of Medicine in 1934. He was a member of the staffs of Holyoke and Providence hospitals, and was a fellow of the American Medical Association.

His widow and a son survive.

MENDENHALL — Walter L. Mendenhall, M.D., of Des Moines, Iowa (formerly of Cambridge, Massachusetts), died on January 18. He was in his sixty-second year.

Dr. Mendenhall received his degree from Drake University College of Medicine in 1906. He was emeritus professor of Pharmacology at Boston University School of Medicine and a retired fellow of the Massachusetts Medical Society.

He is survived by his widow, a son and a grandson.

MONTAGUE — Charles E. Montague, M.D., of Wakefield, died on January 14. He was in his eighty-seventh year.

Dr. Montague received his degree from Boston University School of Medicine in 1896. He was formerly school physician, chairman of the Wakefield Board of Health, assistant in clinical medicine, Boston University School of Medicine, a director of the Southern Middlesex Health Association and a supervising censor of Middlesex East District Medical Society, and was a fellow of the American Medical Association.

He is survived by two nieces and a cousin.

NASON — Arthur C. Nason, M.D., of Newburyport, died on March 23, 1952. He was in his ninety-fourth year.

Dr. Nason received his degree from Columbia University College of Physicians and Surgeons in 1884. He was formerly visiting physician at Anna Jaques Hospital, and was a fellow of the American Medical Association.

SIMMONS — Hannah C. Simmons, M.D., of Worcester, died on January 11. She was in her seventy-sixth year.

Dr. Simmons received her degree from Tufts College Medical School in 1902.

She is survived by a sister, two nephews and two nieces.

CORRESPONDENCE

RESTORATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held January 15, 1953, it was voted to restore the registration of Dr. James W. Elliott, of Boston.

ROBERT C. COCHRANE, M.D.
Secretary

State House
Boston

PERIODIC REGISTRATION OF PHYSICIANS

To the Editor: The statement in the third paragraph of the editorial in the December 11 issue of the *Journal* that "the majority of physicians who have an active say in the Society's deliberations . . . favored the concept of annual registration" does not accord with my information. I have had intimate exposure to the facts for many years, and I have never believed that to be true. I have carefully considered the situation with responsible officers every time it came up and have never myself been persuaded.

It is not, in my view, a forceful argument to say that because bureaucracy has covered all but the doctors it should now be extended to them. The tax commissioner needs more money, but I would rather be taxed where the monies collected by the State could provide funds without these administrative costs. My information has been that the Board of Registration in Medicine already makes a profit from receipts (which it is not allowed to spend for its own administration, but which must go into the general funds of the Commonwealth). What assurance do we have that there would be any better, or enough better, "figures on availability and distribution of physicians" if we added this burden?

Some years ago there was a committee of the Council that did a first-class study of the records of the Board and found them so inadequate that the Council voted, with prolonged applause, to send a copy of the report to the Governor. The failure to utilize available figures by the Board was a surprising demonstration of inefficiency. The existing and available information has never been properly utilized to provide a more adequate list of physicians. It should be remembered that every physician is already required to register with the local board of health. I can think of other, related sources that need not be included in this communication.

The last time this matter came up, it was my stated conviction that the Society should take no favorable action until the previous committee report was reviewed and brought up to date to determine whether the probable yield would justify the various costs. The burden is on the proponents to get the facts to support their contention. Let us have no more government without due consideration!

ELMER S. BAGNALL, M.D.

Groveland, Massachusetts

ANNUAL REGISTRATION OF PHYSICIANS

To the Editor: Relative to the $5 tax on physicians for annual registration, the Board of Registration in Nursing lists nurses for $1 a year and the Board of Registration in Dentistry lists dentists for $2. Now the Board wants $5 for doctors. Why? The civil defense alibi is out, for the dentists are already listed for $2 a head. I should be glad to list the 6000 or 7000 physicians each year for $1 a head. Have you any reason to think the tax will stop at $5 a year?

It used to cost $10 a year for membership in Worcester Medical Society, Massachusetts Medical Society and A. M. A. Now it costs $63.

Remember the modest beginning of the Income Tax.

I should not be surprised to have to pay $100 a year for registration within a few years, and the younger men may live to be taxed $1,000 a year for the privilege of practicing medicine. It is no more fantastic than other changes in our government in the last few years. With our eyes fixed on the Iron Curtain we may have missed important events at home.

MILMAN PEASE, M.D.

Brookfield, Massachusetts

PISTOL-SHOT SOUND

To the Editor: In the November 13 issue of the *Journal*, Dr. F. W. Palfrey states that the pistol-shot sound, representing the water-hammer shock of aortic insufficiency, which is heard when the stethoscope is placed over the radial artery, has never, to his knowledge, been reported. This auscultatory sign is well known in England at least. Sir Thomas Lewis describes it in his book, *Diseases of the Heart* (Third edition. New York: Macmillan, 1944).

I. J. PATTON, M.D.
Associate Director
Medical Literature

Lederle Laboratories Division,
American Cyanamid Company
Pearl River, New York

Note: As Dr. Palfrey stated in his article, the pistol-shot sound is commonly mentioned in reference to the femoral artery, in the groin. Its possible occurrence in other locations, although mentioned by Lewis, is rarely recognized in current teaching in this country. — ED.

THE NUFFIELD TRUST

To the Editor: The considered note by John Lister on Lord Nuffield and his benefactions to medicine and science in the December 4 issue of the *Journal* serves to recall an incident of 1916, long dormant in memory, but easily visualized again into a picture of war-torn Oxford, an overworked consultant, a young physician and a skilful mechanic.

Sir William Osler, a colonel in the Royal Army Medical Corps, had many arduous duties in the autumn of 1916, but one that always gave him unfailing pleasure was a weekly trip by automobile to some nearby Canadian or British hospital. Although petrol was drastically rationed, he was able to obtain a minimum amount for use in his small car, and he looked forward to those relaxing trips, free for a few hours from telephone or visitor. Slim and dapper in a not unbecoming uniform, a pile of book catalogues by his side, Osler was always the gracious host to the young physician who went with him. As the beautiful English countryside quickly slid by, while catalogues were marked and letters read, a scrambled but lively discourse of stories and anecdotes, frequently inspired from some historical tag from a booknote, punctuated the periods of reading and contemplation. So to the hospital, with cheery greetings, a walk through the wards, luncheon accompanied by much banter and wit, lightening up those often dreary rounds and meals. Then the drive back to 13 Norham Gardens, with mind full of plans for actions designed to make someone's life less careworn or more profitable.

But the car was old, sometimes balky and occasionally so temperamental as not to start at all. Then the cry went up: "Get Willie! Get Willie! He can fix anything." And Willie could. I can see him now, small and dark, with keen eyes and an engaging smile, strong and capable hands, coming out from under the car, which he had quickly put right and standing quietly, touching his hat, as we, slowly turning out of the narrow drive, left the house, the motor gently purring. Osler would wave a friendly farewell to the straight young man, former owner of a bicycle shop and now, Willie Morris, proprietor of the local garage.

Osler had great respect for Morris and saw in him something many others overlooked. One morning after a particularly rapid adjustment of the car, Osler turned to a young physician and said, earnestly and thoughtfully, as we left Willie standing by the front door: "That man will go a long way." Did he see in those thoughtful eyes the future Lord Nuffield, the stalwart defender of all that is best in medicine, education and philanthropy? One will never know, but Osler's prophecy that rang out so distinctly on that October morning was certainly clairvoyant, although even he could hardly have estimated what a "long way" that oilstained mechanic would go.

HENRY R. VIETS, M.D.

Boston

FLATTERY, THAT IS

To the Editor: After resolving many times to do so without result, I have been precipitated finally by your editorial entitled "Baker's Dozen, 1953," and the advent of the new year, into writing a few words to express my joy in the

editorials published in the *Journal*. They are not only thoughtful, informative, pertinent and eminently fair, but also sparkling, witty and minor masterpieces of composition. They are the frosting on the nourishing cake of valuable Medical Progress reports, interesting clinicopathological conferences and well selected original articles. Reading them is a few medical moments to which to look forward with delight and anticipation each week.

Now, having flattered you, as was intended without ulterior motive, I should like to make a suggestion. In the case records of the Massachusetts General Hospital in which the diagnosis is primarily cardiac, or in which the electrocardiogram assumes more than an incidental position as a diagnostic tool or is of unusual interest in itself, the reproduction of the record would add much to the presentation. Often, the descriptions given seem inadequate, and even if they are not, there is frequently as much room for varying interpretations of these records as there is of x-ray films.

NORMAN J. SISSMAN, LT. (J.G.) (MC) USNR
Philadelphia

Note: The editor of the Case Records agrees with Dr. Sissman so far as the Case Records are concerned. — ED.

BOOK REVIEWS

International Health Organizations and Their Work. By Neville M. Goodman, M.A., M.D., Camb., F.R.C.P. Lond., D.P.H. Lond. Univ. With a foreword by Sir W. Wilson Jameson, G.B.E., K.C.B., M.D., F.R.C.P., D.P.H. 8°, cloth. 327 pp., with 53 illustrations. Philadelphia: Blakiston Company, 1952. $6.50.

This excellent history covers the early period of quarantine designed to combat epidemics, the international sanitary conferences and conventions from 1851 to 1951, the foundation of the International Office of Public Health in 1907 in Rome and its subsequent development, the Health Organization of the League of Nations (1921–1946), UNRRA, the International Health Conference held in New York in 1946 and the establishment and work of the World Health Organization up to the present time. The book is authoritative, in that the writer has served in recent years on the governing bodies of all the international organizations. Official references to acts and charters, full bibliographies, pertinent illustrations and sound indexes make this volume indispensable as a work of reference. As a history it is sound; as a stirring narrative of remarkable progress, the book has much to offer. The illustrations are of particular value to the historian, but the main use will be for reference. In that respect it is unique and outstanding as a splendid example of completeness, readability and efficient organization of widely scattered material.

HENRY R. VIETS, M.D.

Child Psychiatric Techniques: Diagnostic and therapeutic approach to normal and abnormal development through patterned, expressive, and group behavior. By Lauretta Bender, M.A., M.D. 8°, cloth, 335 pp., with 74 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $8.50.

This book will be of interest to all those in psychiatry and allied fields. It is a collection of papers written by Paul Schilder, Lauretta Bender and their associates at the Bellevue Hospital during the past fifteen years. An honest attempt has been made to portray realistically the methods utilized in the treatment of children.

There is not only a sensible description of various technics but also a discussion of the significance of the phenomena found in creative dancing, abstract drawing and the various forms of play, art and clay modeling. In addition, the author and contributors elaborate upon the genesis, maturation and deviations of the visual motor *Gestalten*. The case material has been chosen wisely and serves to enhance the description of the various therapies. The book gives a short history of the evolution of child psychiatry and then illustrates how diversified one's perspective must be to understand what is being undertaken in the treatment of children.

In summary, this is a worthwhile book for those interested in child psychiatry.

JAMES A. SMITH, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Thyroid. By Thomas H. McGavack, M.D., professor of clinical medicine, New York Medical College, and director, New York Medical College Metropolitan Hospital Research Unit. With a section on surgery by James M. Winfield, M.D., professor and director of surgery, New York Medical College; and Walter L. Mersheimer, M.D., associate professor of surgery, New York Medical College; and a section on history, by Dorothy B. Spear, Ph.B., and Thomas H. McGavack. 8°, cloth, 646 pp., with 72 illustrations and 22 tables. St. Louis: C. V. Mosby Company, 1951. $13.50.

This new book on the thyroid gland covers the subject in all its aspects. The material is divided into four main sections: history; anatomy, chemistry, and physiology; morbid states; and surgery. The history of the thyroid gland from the earliest times to the present comprises 49 pages. One of the co-authors of this section, Miss Spear, will be remembered as a former reference librarian of the Boston Medical Library. The literature has been surveyed, and extensive bibliographies have been appended to the sections. There is a good index of subjects, and the publishing is excellent. A type pleasing to the eye has been used throughout the book, which should be in all collections on the endocrines.

A Textbook of Pharmacology: Principles and application of pharmacology to the practice of medicine. By William T. Salter, M.D., professor of pharmacology, Yale University School of Medicine. 4°, cloth, 1240 pp., with 284 illustrations. Philadelphia: W. B. Saunders Company, 1952. $15.00.

This new book might well be called an applied pharmacology, stressing the clinical aspects of the subject. It is a personal book, reflecting the opinions of the author, gained over a long period. The text is divided into four chief categories: general principles; drug action on physiologic mechanisms; the application of drugs in clinical medicine; and toxicology. Short lists of selected references are appended to the various chapters. There is a comprehensive index, and the publishing is excellent.

Lung Abscess. By R. C. Brock, M.S., F.R.C.S., thoracic surgeon to Guy's Hospital, and surgeon to the Brompton Hospital. 8°, cloth, 197 pp., with 60 illustrations. Springfield, Illinois. Charles C Thomas, 1952. $7.75.

Mr. Brock discusses lung abscess in its different aspects: types, etiology and treatment. The monograph is well illustrated. There is a good index, a bibliography, and the publishing is fine in every way. The printing was done in Great Britain for Blackwell. The monograph is recommended for all collections on diseases of the lungs.

NONCLINICAL NOTES

CHAIRMAN OF RED CROSS DOCTORS DIVISION

Dr. Louis K. Diamond, director of the research hematology laboratory, blood-grouping laboratory and blood bank at Children's Medical Center and associate professor of pediatrics at Harvard Medical School, has been named chairman of the Doctors Division for the 1953 Greater Boston Red Cross Fund.

He is a member of the advisory committee to the president of the American National Red Cross in the operation of the Red Cross Blood Program. As director of the Blood Program, Washington, D. C., from February, 1948, through October, 1950, Dr. Diamond was instrumental in the growth of the nationwide program, which has been a national asset, reflected in the help given to men wounded in Korea, the civilian sick and injured, and the plasma stockpile for military and civilian emergencies.

NOTICES

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The annual meeting of the New England Society of Anesthesiologists will be held in the Joslin Auditorium of the New England Deaconess Hospital, Boston, on April 10.

PROGRAM

Morning Session:

8 a.m.–12 m.

Operative clinics in any hospital Society members wish to visit.

Afternoon Session:

1:30–5 p.m.

Anesthesia for Intracardiac Surgery.
Dr. William S. Derrick, director of anesthesiology, Peter Bent Brigham Hospital.

Anesthesia for the Diabetic Patient.
Dr. Priscilla White, Joslin Clinic, New England Deaconess Hospital.

Anesthesia for Oral Surgery.
Dr. Walter Guralnick, visiting instructor in oral surgery, Tufts College Medical School; and Dr. John Sheehan, Department of Anesthesiology, Boston City Hospital.

Technics of Regional Anesthesia. A motion picture in color and sound presented by Drs. John Bonica and Daniel Moore (through the courtesy of Winthrop-Stearns, Incorporated).

Evening Session:

7–7:30 p.m.

Business Meeting.

7:30–8:30 p.m.

Application of Pulmonary-Function Studies to Anesthesia.
Dr. Edward A. Gaensler, research fellow, Thorndike Memorial Laboratory, Boston City Hospital, and Department of Medicine, Harvard Medical School; instructor in surgery, Boston University School of Medicine, and assistant visiting surgeon (thoracic), Boston City Hospital.

8:30–9 p.m.

Discussion.

AMERICAN COLLEGE OF CARDIOLOGY

The second annual convention of the American College of Cardiology will be held at the Statler Hotel, Washington, D. C., on June 7, 8 and 9. The topic of the meeting will be "Diagnosis of Cardiac Diseases." Guest speakers of national prominence will cover all aspects and methods of cardiac diagnosis. In addition to the scientific sessions, there will be scientific exhibits on cardiovascular research and thirty-six commercial exhibits, outlining the latest advances in cardiac instrumentation, pharmacology and therapy, and displaying recent publications in the field of cardiology. Further information regarding the program, may be obtained from the Secretary, Dr. Philip Reichert, 480 Park Avenue, New York 22, New York.

FOURTH SUPPLEMENT TO MOTION PICTURE REVIEWS NOW AVAILABLE

The Committee on Medical Motion Pictures of the American Medical Association has completed the fourth supplement to the booklet entitled "Reviews of Medical Motion Pictures." It contains all the film reviews published in the *Journal of the American Medical Association* from January to December, 1952. The purpose of the reviews is to provide a brief description and evaluation of motion pictures available to the medical profession. All films are reviewed by competent authorities.

One copy has been mailed to the secretary of each state medical society. Copies are available to county medical societies on request to the Committee on Medical Motion Pictures, American Medical Association, 535 North Dearborn Street, Chicago 10.

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held at the Hotel Shelton on Wednesday, March 4. Dinner will be served at 6:30 p.m. Nonmembers and guests are invited to hear the speakers at 8 p.m., when a symposium on migraine and tension headaches will be presented.

PROGRAM

Diagnosis and Physiological Mechanisms. Dr. John R. Graham, chairman.
Medical Management. Dr. F. Dennette Adams.
Surgical Management. Dr. William H. Sweet.
Psychiatric Aspects. Dr. Mandel E. Cohen.

BOSTON EVENING CLINIC

A staff meeting of the Boston Evening Clinic will be held at the Clinic Building on March 17, at 8 p.m. A discussion period will follow the program.

PROGRAM

Surgical Physiology of the Thyroid Gland. Dr. Norman Lenson.
Current Concepts Concerning the Management of Hyperthyroidism. Dr. Manuel Kaufman.
Current Advances of Endocrinology of the Thyroid Gland. Dr. Vaughn Westermeyer.
The Thyroid Adenoma. Dr. Edward J. Palmer.

Physicians and medical students are invited.

NEW ENGLAND CENTER HOSPITAL HOUSE OFFICERS' ASSOCIATION

A meeting of the New England Center Hospital House Officers' Association will be held in the Stearns Auditorium of the Hospital on Friday, March 13, at 7 p.m. Dr. John S. L. Browne, professor of medicine, McGill University Faculty of Medicine, and director, McGill University Clinic, Royal Victoria Hospital, will speak on the subject "Changing Aspects of Medicine." Discussers will be Drs. Edwin B. Astwood and J. H. Means.

All interested persons are invited to attend.

HARVARD UNIVERSITY CAREER CONFERENCE IN THE MEDICAL SCIENCES

A career conference in the medical sciences to help students decide on their careers after graduation will be held at Dudley Hall, Harvard University, Cambridge, on Tuesday, March 10, at 8 p.m., with Dr. George P. Berry, dean of Harvard Medical School, as chairman.

One of a series of nine conferences on various careers, this conference is open to the public.

NEW ENGLAND PEDIATRIC SOCIETY

The annual meeting of the New England Pediatric Society will be held on Wednesday, March 11. The usual clinical activities will be presented during the day in the auditorium of the Jimmy Fund Building.

The evening meeting will be held at Longwood Towers.

MASSACHUSETTS SOCIETY OF ANESTHESIOLOGISTS

A meeting of the Massachusetts Society of Anesthesiologists will be held in the Joslin Amphitheater of the New England Deaconess Hospital, Boston, on Friday, March 6, at 7:30 p.m. A panel on the adrenal cortex and its relation to surgery and anesthesia will be presented.

PROGRAM

Physiology of the Adrenal Cortex. Dr. Dalton Jenkins, instructor in medicine, Harvard Medical School, and junior associate in medicine, Peter Bent Brigham Hospital.

Response of the Adrenal Cortex to Surgery and Anesthesia. Dr. David Hume, instructor in surgery, Harvard Medical School, and junior associate in surgery, Director of Laboratory for Surgical Research, Peter Bent Brigham Hospital.

Anesthetic Problems Observed in Patients with Adrenocortical Dysfunction. Dr. William S. Derrick, associate in anesthesia, Harvard Medical School, and anesthesiologist, Peter Bent Brigham Hospital.

An informal dinner will be held at Simpson House, 1114 Beacon Street, Newton Center, at 5:30 p.m.

SPRINGFIELD HOSPITAL EDUCATIONAL PROGRAM

The Educational Program of the Springfield Hospital for the month of March is as follows:

Monday, March 2

6:30 p.m. Laboratory Pitfalls. Staff Conference Room. Dr. Allen S. Johnson.

Friday, March 6

11 a.m.–12 m. Grand Medical Rounds, Staff Conference Room.

6:30 p.m. Supportive Therapy of a Surgical Patient Exclusively by Parenteral Fluids. Staff Conference Room. Dr. Ahmad Nakib.

Saturday, March 7

8:30–10 a.m. Surgical Service Conference, classroom, second floor.

10–11 a.m. Grand Surgical Rounds, Staff Conference Room.

11 a.m.–12 m. Demonstration of the Use of Plastic Fenwal Equipment in a Disaster. Staff Conference Room.

Monday, March 9

6:30 p.m. Surgical Conditions of the Pancreas. Staff Conference Room. Dr. James V. Scola.

Friday, March 13

11 a.m.–12 m. Grand Medical Rounds, Staff Conference Room.

6:30 p.m. Jaundice, Differential Diagnoses. Staff Conference Room. Dr. Omar T. Pace.

Saturday, March 14

8:30–10 a.m. Surgical Service Conference, classroom, second floor.

10–11 a.m. Grand Surgical Rounds, Staff Conference Room.

11 a.m.–12 m. Clinicopathological Conference, Staff Conference Room.

Monday, March 16

6:30 p.m. Aneurysm and Arteriovenous Fistulas. Staff Conference Room. Dr. Field C. Leonard.

Friday, March 20

11 a.m.–12 m. Grand Medical Rounds, Staff Conference Room.

6:30 p.m. Surgery of the Adnexa. Staff Conference Room. Dr. Robert J. Carpenter, Jr.

Saturday, March 21

8:30–10 a.m. Surgical Service Conference, classroom, second floor.

10–11 a.m. Grand Surgical Rounds, Staff Conference Room.

11 a.m.–12 m. Medical Death Review, Staff Conference Room.

Monday, March 23

6:30 p.m. Differential Diagnoses of Cystic Diseases of the Chest. Staff Conference Room. Dr. Frederick A. Post.

Wednesday, March 25

1 p.m. Pediatric Conference, Staff Conference Room.

Friday, March 27

11 a.m.–12 m. Grand Medical Rounds, Staff Conference Room.

6:30 p.m. Colostomy Care. Staff Conference Room. Dr. Omar T. Pace.

Saturday, March 28

8:30–10 a.m. Surgical Service Conference, classroom, second floor.

10–11 a.m. Grand Surgical Rounds, Staff Conference Room.

11 a.m.–12 m. Surgical Death Review, Staff Conference Room.

Monday, March 30

6:30 p.m. Differential Diagnoses of Tumors of the Neck and Their Treatment. Staff Conference Room. Dr. W. Fenn Hoyt.

Every Wednesday, from 11 a.m. to 12 m., a psychosomatic and group-psychotherapy conference is held in the Staff Room under the direction of Dr. Calvert Stein. Every Thursday, from 3 to 4 p.m., a pathology conference is held in the Staff Conference Room.

ALUMNI ASSOCIATION OF THE STATE UNIVERSITY COLLEGE OF MEDICINE AT NEW YORK CITY

The annual alumni day of the State University College of Medicine at New York City will take place on Saturday, April 25. A scientific session will be held at the Polhemus Clinic, followed by the annual business meeting. Luncheon will be served. The seventy-third annual dinner, at the Hotel Granada, Ashland Place and Lafayette Avenue, Brooklyn, New York, will begin at 7 p.m.

PHI DELTA EPSILON LECTURE

The Tufts College Medical School chapter of the Phi Delta Epsilon medical fraternity will present its annual lecture in the auditorium of the Beth Israel Hospital, on Wednesday, March 4, at 8 p.m. Dr. Isadore Snapper, director of medical education, Cook County Hospital, Chicago, Illinois, will speak on the subject "Medical Bone Diseases."

Physicians and medical students are invited to attend.

SOCIETY MEETINGS AND CONFERENCES

February 26–28. American Academy of Allergy. Page 354, issue of February 19.

February 27–March 27. Combined Anesthesia Teaching Conferences of Boston. Page 210, issue of January 29.

March 2. New England Cardiovascular Society. Page 308, issue of February 12.

March 2 and 3. Massachusetts Trudeau Society and the American College of Surgeons. Hotel Statler, Boston.

March 2–5. Sectional Meeting of American College of Surgeons. Hotel Statler, Boston. Page 350, issue of February 19.

March 2–5. New Orleans Graduate Medical Assembly. Page 828, issue of November 20.

March 2–27. Consultation Clinics for Crippled Children in Massachusetts. Page 353, issue of February 19.

March 2–30. Springfield Hospital Educational Program. Notice above.

March 2–April 20. Hartford Medical Society. Page 42, issue of January 1.

March 2–May 4. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 540, issue of October 2.

March 3. Boston City Hospital House Officers' Association. Page 353, issue of February 19.

March 4. Phi Delta Epsilon Lecture. Notice above.

March 4. Greater Boston Medical Society. Page 395.

March 4. Massachusetts School Physicians' Association. Page 266, issue of February 5.

March 4–April 8. Postgraduate Medical Institute. Boston. Page 452, issue of September 18.

March 6. Massachusetts Society of Anesthesiologists. Page 395.

March 7. Antibiotics: Specific Indications. Drs. Maxwell Finland and Louis Weinstein. Mount Auburn Hospital, Cambridge. 10:05 a.m.

March 8–10. Alumni Postgraduate Convention. College of Medical Evangelists. Page 266, issue of February 5.

March 9 and 23. Postgraduate Course in General Medicine. Cushing Veterans Administration Hospital, Framingham. Page 697, issue of October 30.

March 10. Harvard University Career Conference in the Medical Services. Page 395.

March 10. Harvard Medical Society. Page 353, issue of February 19.

March 11. New England Pediatric Society. Page 395.

March 11 and April 1. Postgraduate Medical Institute Course in General Medicine. Burbank Hospital, Fitchburg. Page 1049, issue of December 25.

March 12. Pentucket Association of Physicians. Pentucket Club, Haverhill. 8:30 p.m.

March 13. Gardner Postgraduate Seminar. Henry Heywood Memorial Hospital, Gardner. 6:00–8:00 p.m.

March 13. New England Center Hospital House Officers' Association. Page 395.

March 17. Boston Evening Clinic. Page 395.

March 17. South End Medical Club. Page 307, issue of February 12.

March 25. Cutter Lecture. Page 307, issue of February 12.

March 25. Graduate Club of Boston, Phi Delta Epsilon Medical Fraternity. Page 307, issue of February 12.

April 3. New England Society of Anesthesiologists. Page 418, issue of September 11.

(*Notices concluded on page xiii*)

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(*Additional advertisements on page xii*)

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NOTICES (*Concluded from page 396*)

APRIL 10. New England Society of Anesthesiologists. Page 395.

APRIL 10–12. American Association of the History of Medicine. Page 308, issue of February 12.

APRIL 15. Massachusetts Academy of General Practice. Spring Clinical Assembly. Hotel Shelton, Boston.

APRIL 16–18. Boston Lying-in Hospital Postgraduate Course in Obstetrics and Pediatrics. Page 307, issue of February 12.

APRIL 19–24. National Industrial Health Conference. Page 308, issue of February 12.

APRIL 25. Alumni Association of the State University College of Medicine at New York City. Page 396.

APRIL 25. Graduate Club of Boston, Phi Delta Epsilon Medical Fraternity. Page 307, issue of February 12.

APRIL 29 AND OCTOBER 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.

MAY 19–21. Massachusetts Medical Society. Hotel Statler, Boston.

MAY 25–31. First World Congress on Fertility and Sterility. Page 1001, issue of December 18.

JUNE 7–9. American College of Cardiology. Page 395.

District Medical Societies

ESSEX NORTH

MAY 13. Andover Country Club, Shawsheen.

MIDDLESEX SOUTH

MARCH 7. Margaret Jewett Hall, Mount Auburn Hospital. 10:05 a.m.

MIDDLESEX WEST

MARCH 9 and 23. Postgraduate Course in General Medicine. Cushing Veterans Administration Hospital, Framingham.

NORFOLK

MARCH 24.

Calendar of Boston District for the Week Beginning Thursday, March 5

THURSDAY, MARCH 5

Sectional Meeting, American College of Surgeons. Hotel Statler.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Cardiac Grand Rounds. Main Amphitheater, Children's Medical Center.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, MARCH 6

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Dr. George W. Thorn and Dr. Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.
*7:00–9:00 p.m. Combined Anesthesia Teaching Conference of Boston. Amphitheater, Evans Memorial, Massachusetts Memorial Hospitals, Eighth Floor, 65 East Newton Street.
7:30 p.m. Massachusetts Society of Anesthesiologists. Joslin Amphitheater, New England Deaconess Hospital.

SATURDAY, MARCH 7

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
10:05 a.m. Mount Auburn Hospital Panel Discussion. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, MARCH 9

*8:00–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*2:00–8:30 p.m. Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital, Waltham.
*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

TUESDAY, MARCH 10

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
11:00 a.m.–12:00 m. Regular Grand Rounds of the Pediatric Department. Dowling Amphitheater, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*8:00 p.m. Harvard University Career Conference in the Medical Sciences. Dudley Hall, Harvard University, Cambridge.
8:00 p.m. Harvard Medical Society. Amphitheater, Building D, Harvard Medical School.

WEDNESDAY, MARCH 11

Annual Meeting, New England Pediatric Society. Clinical activities during the day. Auditorium, Jimmy Fund Building, 25 Binney Street. Evening Meeting, Longwood Towers.
*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Medical Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheater, New England Deaconess Hospital.
*4:00 p.m. Thoracic Conference. Held by Overholt Clinic. Harris Hall, New England Deaconess Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*7:30 p.m. Lahey Clinic Lecture. Chest Diseases. Drs. Carlton R. Souders, David P. Boyd and Stewart H. Jones. Joslin Auditorium, New England Deaconess Hospital.

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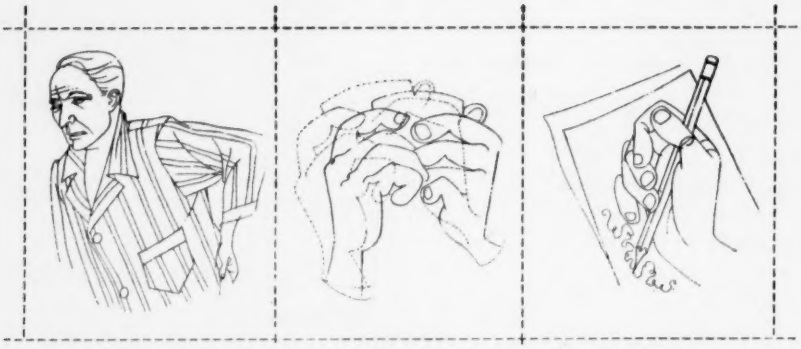

in muscle spasm of rheumatic disorders | **in acute alcoholism** | **in certain neurologic disorders**

The new, uniform oral dose for adults is 1-3 grams. This may be repeated 3-5 times per day.

The first dose prescribed should be at the lower end of the recommended dosage range *(an occasional patient may complain of side effects when* large *doses are given at the* start *of Tolserol therapy).* Subsequent doses may be adjusted to the needs of the individual patient. Whenever possible, Tolserol should be given after meals. When Tolserol is given between meals, it is desirable that the patient first drink ⅓ glass of milk or fruit juice.

UNIVERSITY MICROFILMS
313 N. FIRST ST.
ANN ARBOR MICH.

Tolserol

Squibb Mephenesin

Tablets, 0.5 Gm. and 0.25 Gm., bottles of 100; *Capsules,* 0.25 Gm., bottles of 100; *Elixir,* 0.1 Gm. per cc., pint bottles; *Intravenous Solution,* 20 mg. per cc., 50 cc. and 100 cc. ampuls.

"TOLSEROL" (REG. U. S. PAT. OFF.) IS A TRADEMARK OF E. R. SQUIBB & SONS

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